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The Archives of Internal Medicine

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MULTIPLE ABSCESSES OF THE BRAIN IN INFANCY*

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During the past year the following case, that proved to be multiple abscesses of the brain, and that, clinically, was practically undifferentiable from chronic internal hypdrocephalus, came under observation. Certain unusual features make it worthy of reporting. The clinical history of the case was as follows:

REPORT OF CASE

History.—T. D., a white male infant, aged 23 months, was brought to the Harriet Lane Home in the service of Dr. John Howland, Oct. 27, 1914, with the complaint "Large Head." The change had been first noticed when the child was 18 months old.

Family History.—Father and mother living and well at 46 and 23 years, respectively; two other children, aged 5 and 3, living and well; no history of miscarriages, or of tuberculosis.

Previous History.—Full term, noninstrumental birth. Pregnancy, the third; labor rather hard (pains being present for two days before the child was born). Infant apparently normal and healthy. Weight about 9 pounds.

The child was breast fed for two months, and then given diluted cow's milk with sugar. He always took his food well. Other articles were added to his diet at 15 months.

He cut his teeth at 5 months, sat up at 6 months, and walked and said a few words at 15 months. He had a severe attack of pertussis at 7 months, apparently without after effects. There had never been any evidence of middle ear affection.

He stopped walking and talking at 16 months, and two months later it was noticed that his head was enlarged. During the six weeks preceding admission, the head was said to have increased a good deal in size. The child had never had convulsions. There was no history of injury or trauma.

Examination.—The child was admitted to the hospital October 27 as a well-nourished, well-developed boy, 74 cm. in length, inattentive and with an expressionless face. He closed his eyes or turned away his head if light was flashed in his face and did not grasp objects. His head was large, the circumference 52 cm. It was much wider through the parietal diameter than through the frontal diameter, so that viewed from above, it was rather triangular in shape, with the apex at the forehead. The forehead bulged, giving the impression that the eyes were sunken. The anterior fontanel measured 3 x 3 cm., and was situated further back than normal. It was tense, but not

* Submitted for publication Jan. 12, 1916.

* From the Department of Pathology of the Johns Hopkins Hospital and University.

Fig. 1.—Sagittal section of brain showing abscess. Two-thirds natural size; section taken from *x*.

bulging; pulsation was transmitted. The sagittal suture was ununited and moveable, becoming soft and yielding at the posterior fontanel. The other sutures were firmly united. The superficial veins, particularly over the frontal and lateral regions of the skull, were prominent. The eyes appeared deeply placed, but were not dislocated downward; followed objects well. There was no nystagmus or paralysis. The chest was normal in form, its circumference 47 cm. The heart, lungs and abdomen seemed normal.

On further examination, it was seen that the child grasped objects fairly well with his left hand, but refused to take them with his right hand. If the left arm was held, the child moved the right arm poorly and was not able to eat with it. He took bread well with his left hand, but there was marked tremor as he moved it to his mouth. The difference in the movements of the two hands was quite marked. When the child desired to be taken up, he stretched out his left hand; the right remained still, or, at least, was moved less freely.

Fig 2—Transverse section immediately in front of tips of temporal lobes. Photograph ⅕ natural size. Shows displacement of right lateral ventricle and distortion of other structures; also relative enlargement of left hemisphere.

The reflexes in both arms and the knee jerks were exaggerated and equal. The cremasteric reflexes were present. There was no spasticity in the arms or the legs. There were no contractures. The Babinski was negative. A fairly sustained ankle clonus was obtained at times. The child did not speak but seemed to understand what was said to him. Sensation was present and equal on the two sides, so far as could be determined.

Temperature, on admission, 99 F.; pulse, 140 to 160; respiration, 28; white count, 10,000; urinary examination, negative; Roentgen-ray report as follows: "Head markedly deformed, external hydrocephalus—sella shows evidence of pressure." Lumbar puncture yielded 25 c.c. of clear fluid apparently under increased pressure—(pressure on the anterior fontanel was thought to increase the rate of flow)—and containing 7 lymphocytes and many red blood cells per

cubic centimeter; globulin test positive. The Wassermann test (blood and spinal fluid) was negative. The von Pirquet test was negative.

Operation.—Two ventricular punctures were made about six days apart (Dr. Dandy). Attempts to enter the left ventricle and the third ventricle were unsuccessful. Puncture of the right ventricle yielded a few drops of blood, tinged, it was thought, with cerebrospinal fluid and followed by freely flowing, dark, red blood. A sense of increased resistance felt on the right side suggested the presence of brain tumor. It was not felt that the ventricles were dilated.

A second lumbar puncture (November 5) yielded 10 c.c. of fluid with 35 cells per c.mm. A positive globulin test was obtained.

The phenolphthalein test done at this time showed an excretion within normal limits.[1]

Fig. 3.—Transverse section half way between tips of temporal lobes and anterior border of pons. Photograph ⅘ natural size. Shows displaced ventricles and median structures, large size of left hemisphere, and beginning of abscess cavity.

The condition of the child remained unchanged. The temperature remained normal. The white count remained low. There was no perceptible increase in the size of head after admission.

Exploratory Craniotomy.—(Dr. Heuer). The skull was thin; the dura was not adherent. A needle was inserted into the frontal area, which appeared relatively softer; a little fluid escaped from the path left after withdrawing the needle. It was apparently under no pressure. The opening was enlarged by blunt dissection until a good exposure of the ventricle (right lateral) was obtained. The ventricle appeared to be definitely enlarged (diameter 7.5 cm.)

1. Dandy, Walter E., and Blackfan, Kenneth, D.: Internal Hydrocephalus, An Experimental, Clinical and Pathological Study, Am. Jour. Dis. Child, 1914, viii, 406.

and could be followed practically to the posterior limit, and also anteriorly for quite a distance. On vacating the field opening on the cortex closed over through sagging, "drooping," in of its walls due to release of the fluid tension within. The membranes and bone flap were closed as usual.

Postoperative Course.—Following the operation, the child was not able to use either the left arm or leg; and by the third night, these had both become spastic. The temperature remained elevated, 104 to 106; the pulse was rapid. The child was often restless and often made purposeless movements. His eyes deviated to the left. Edema of the *right* eye appeared on the fifteenth day and became marked; on the sixteenth day the child was unable to close his *left* eye. The leukocytes at this time reached 22,600. Jerky movements appeared in the right arm and leg. The temperature rose to 106.5 at midnight of the sixteenth, and the child died at 4:15 a. m., November 17.

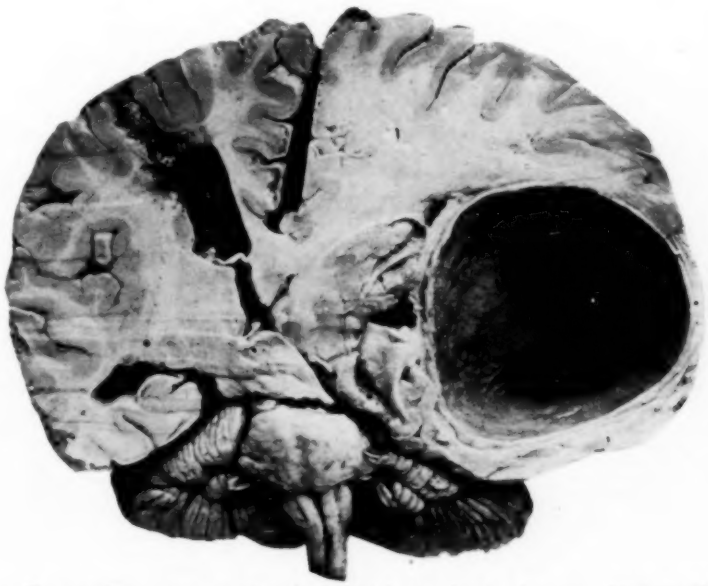

Fig. 4.—Transverse section immediately in front of pons. Photograph, ½ natural size. Showing operative wound; large right lateral ventricle; obliterated left lateral ventricle; large abscess cavity with thick pyogenic membrane. A second section half way to the tip of the posterior lobe is seen to pass through the posterior wall of the cavity, and the median wall of the cavity is seen to bulge laterally (due to pressure of a second abscess).

Postmortem Examination (Nine Hours After Death).[2]—When the dura was opened it was seen that the left hemisphere was distinctly larger than the right. The convolutions on the left side were wide and flat. The left occipital lobe was softer than the other portions of the brain, and the dura was slightly adherent at this point. Sections were made of the brain. On transverse section of the hemispheres at the tips of the temporal lobes (Fig. 2), the right ventricle was seen cut across; the left ventricle was not visible.

2. Permission was granted for examination of the brain only.

Section through the temporal lobes at the level of the optic chiasm and parallel to the first section, revealed a *large abscess* in the white matter of the left hemisphere, the anterior wall of the abscess reaching just to the section. (Figs. 2 and 3.) The left ventricle was seen pushed over toward the right and collapsed. The right ventricle appeared a little larger than normal, but its increase in size was not very marked.

A section at the level of the anterior border of the pons (Fig. 4) showed that the abscess involved much of the hemisphere. It measured 6.2 x 5 cm. in the transverse and vertical directions, respectively, and 7.5 cm. in the anteroposterior direction. It was definitely encapsulated, and contained greenish-yellow, purulent material of creamy consistency, homogeneous and not tenacious. The wall of the cavity was firm, apparently composed of dense connective tissue and 3 mm. in thickness. The left ventricle appeared somewhat distended.

The aqueduct of Sylvius had been much dislodged toward the right. There was evidently no communication between the left ventricle, which was collapsed, from direct pressure of the abscess, and the right ventricle,

Fig. 5.—Transverse section half way between plane of Figure 4 and the tip of the occipital lobe, showing second large abscess. Photograph, ½ natural size.

which was perhaps a little distended. The obstruction of the aqueduct of Sylvius might well have caused an internal hydrocephalus.

The conditions found on the right side appeared to be solely those of displacement caused by pressure from the large abscess.

After the pus had been evacuated from the posterior half of the abscess cavity, it was seen that the posterior median wall bulged laterally as a fluctuating tumor. A third section, half-way between the anterior border of the pons and the tip of the occipital lobe and in a plane parallel to those of the previous sections, passed through the posterior portion of the first abscess and diametrically across a smaller one (Fig. 5). This somewhat smaller abscess lay thus mesial to the posterior extremity of the first abscess and projected backward and outward into the occipital lobe. The collapsed condition of the lateral ventricle is well seen in the photograph.

A fourth section made in the same manner as the third, revealed three smaller abscesses in the tips of the occipital lobe (Figs. 4, 5 and 6). The smaller of these had much less definitely organized walls and the distinction between wall and puriform contents was not so well defined.

Preparations from the contents of the larger cavities and from the walls showed no micro-organisms, "acid-fast" or other; nor were any found in the sediment after digestion in a strongly alkaline solution of sodium hypochlorite (antiformin). Cultures were not made owing to the body having been injected with solution of formaldehyd.

Microscopical Notes.—Sections extending through the wall of the cavity and the adjacent brain tissue and taken from a variety of locations all showed essentially the same structure. That taken from the area marked "x" in Figure 1 forms the basis of the following description: As is seen in the figure, the section extends from the inner surface of the dense fibrous wall of the cavity, through it and the compressed brain tissue to the pia. The relations are well shown in the colored drawing made by Mr. Broedel from the microscopical preparation (Fig. 7). In the photograph, a cortical fissure is seen traversing the section: it is displaced by the tumor until it runs almost parallel to the wall of the cavity. In the microscopical preparation, this appears at c′, where a portion of the pia and its vessels is seen lying between areas of compressed cortex.

Fig. 6.—Transverse section half way between plane of Figure 4 and tip of occiptal lobe, showing smaller and less well circumscribed abscesses. Photograph, about ⅔ natural size.

For convenience of description, the section may be divided into layers, or regions.

The cellular exudate (a) or puriform contents of the cavity is seen to consist of mononuclear cells, accompanied by very few polymorphonuclear cells. Many of the mononuclear cells contain globules of lipoid substance that have been more or less deeply stained with sudan III.

The polymorphonuclear cells are few in number; they are typical pus cells.

The mononuclear cells all closely resemble one another, differing only in the amount of stainable lipoid substance that they contain, and in the depth of staining of the nucleus. The nuclei are usually round or ovoid in shape and contain a centrally placed nucleolus and chromatin granules scattered toward the periphery. Some of the nuclei are much more deeply stained than others and in them the arrangement of the chromatin is less evident. Where the accumulation of the lipoid substance is great the nucleus is dis-

placed toward the side of the cell; it may even come to lie on the periphery of a large globule of fat. These nuclei are, in no case, polymorphous (for example, clover-leaf), in form, and the occasional pus cells found seem to be free from the stainable lipoids. Certain ones of the larger fat-containing cells have multiple nuclei; these nuclei resemble the single nuclei.

These large mononuclear cells containing fatty substances and staining more or less deeply with sudan III, are found here and there throughout the section. They appear to be unusually good examples of the phagocytic cells of the central nervous system, the so-called *cerebral granule cells.* They form the most conspicuous and interesting feature of the sections in this case. Their origin will be discussed hereafter.

The wall of the cavity, (b), is formed of dense fibrous tissue. The characteristic cells are long and slender, are tangentially disposed, and intertwine, more or less, with their fellows. The protoplasm has a uniform glassy appearance or is finely granular, and is free from fatty particles. The nuclei are slender, tapering, and closely resemble the nuclei of ordinary connective tissue in form and arrangement of chromatin. In some places small groups of cells are seen to be included in the fibrous wall; these are, in every way, the counterparts of the mononuclear cells composing the exudate described above. The fibrous capsule, as a whole, is conspicuously free from capillaries or cellular inclusions, and appears as a dense membrane composed of long fusiform cells, with infrequent, slender nuclei. Cells like those seen in the exudate occur, however, scattered here and there through this area. Many of the more centrally placed ones stain faintly with sudan III, but as the margins are approached, these myelin-bearing cells become more numerous, and larger, and more deeply staining. The nuclei may become larger, less regular, darker and more diffusely staining.

At the junction of the fibrous layer and the layer of exudate, two distinct types of cells are seen. The first is the typical cell of the exudate; a round or ovoid cell with a round nucleus in which there is a more or less centrally placed nucleolus and peripherally small globular masses of chromatin. When laden with myelin, the appearance of these cells is modified in the manner described above. The second type of cell occurs in much smaller numbers. It has a round, ovoid or elongated, nucleus, several times larger than that of the cell last mentioned, and vesicular in character, with the chromatin scattered rather evenly throughout the nucleus in the form of fine granules. These cells are seen most frequently in close proximity to the delicate capillary processes and appear to be endothelial polyblasts. Every transition between these and the characteristic cells of the fibrous capsule appears to be present. The nuclei of the fat-containing cells are rarely, if ever, found to resemble the nuclei of these cells.

Adjacent to the fibrous capsule and blending with it is a zone of blood vessels (c). These are relatively numerous and large. Branches from them penetrate the fibrous capsule here and there and may be found extending quite to the cellular exudate on the opposite surface. Lymphatic spaces, (d), are seen near the larger vessels. Near some of them are seen also, collections of small round cells. The cells forming these collections are quite distinct from the mononuclear cells forming the exudate described above. Transitional forms are not clearly distinguished.

The figures seen at (c) are small areas of brain tissue much infiltrated with cells and more or less isolated by connective tissue growth. They come thus to resemble "cell nests." The infiltrating cells have irregular, somewhat vesicular nuclei, bearing scattered masses of chromatin of varying sizes, and with, or without, a definite nucleolus. In some of these areas a diffuse reddish staining indicates the presence of minute globules of liquid substances in the degenerating tissue; these globules are here seldom phagocyted.

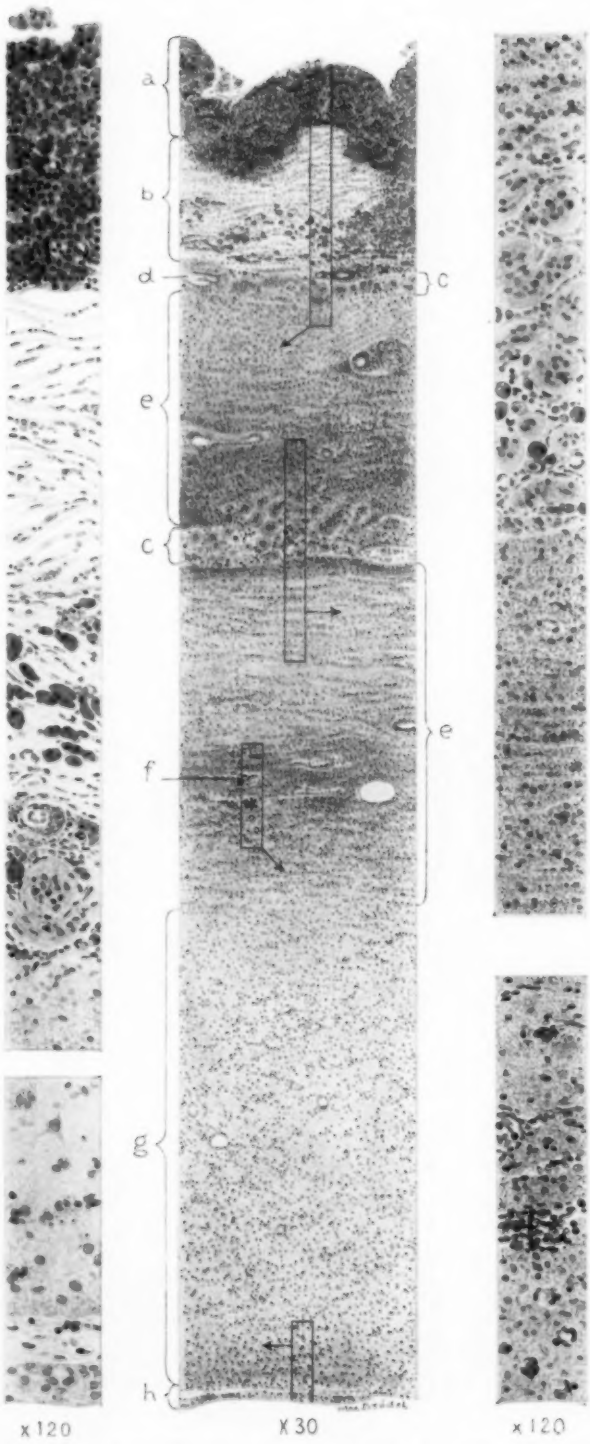

Fig. 7.—Color plate showing microscopic details. For full explanation see text.

Illustrating Article by James B. Holmes, M.D., The Archives of Internal Medicine, May, 1916.

The zone marked (e) is a layer of cerebral tissue that has been compressed and, in a large measure, absorbed. It resembles closely the neighboring area, (e′), and a description of the latter will serve for both. The two areas are separated by an infolding of the pia and its vessels (c′). The figures described under (c) are here seen again.

The zone (e′) is composed in the main of much compressed and degenerated medullary matter. The tissue has a tendency to fall into strands that represent axis cylinders or groups of them, and are tangentially disposed. Fine droplets of lipoid substance stained with sudan III are seen everywhere. Here and there larger aggregates are seen; these are often phagocyted. Large, fat-containing cells become progressively more numerous as the zone (c′) is approached. The total number of cells in the zone is relatively much increased. Of these cells, two types may be recognized: (1) a cell with a large, clear vesicular nucleus, with one or more larger masses of chromatin (nucleoli) and a reticulated appearance; and (2) a cell with a much smaller round nucleus varying much in depth of staining. It is these latter cells that contain phagocyted myelin droplets. The depth of staining of the nucleus here, again, is often proportionate to the amount of phagocyted myelin within the cell. The cells are rather readily classified into these two types, though occasional cells are seen that are intermediate in appearance.

The capillaries in this zone are relatively numerous. This is, in a measure, due to the absorption of degenerated cerebral tissue and the consequent approximation of previously existing capillaries. These vessels are nowhere occluded; there is no accumulation of infiltrating cells in their neighborhood; and no proliferation of the cells in their walls is seen. The endothelial cells in their walls are usually readily distinguishable from the cells of either of the above mentioned groups. Heavily laden "granule cells" are occasionally seen in close proximity to the walls of the capillaries. In some places, fine myelin droplets are seen also in the walls of the capillaries. Usually, they appear free, but sometimes they seem to have been phagocyted by cells within the capillary walls.

In the most superficial zone (g) the number of cells is relatively much less. There is noticeable absence of the minute stained myelin droplets elsewhere seen lying free in the degenerating cerebral tissue, and there appears to be much less injury to the brain substance. The large ganglion cells, however, are usually not well preserved and are infrequently met. Cells of the first type described in zone (e′) are the prevailing cells. The stainable lipoid substances are here present almost exclusively in cells of the second type, and give the body of these cells a faint reddish-yellow tinge, or, where most abundant, completely fill it with a more or less globular mass that stains deeply with sudan III. Many of these smaller cells are seen without such stainable substances in the cell body or in the immediate neighborhood; they have the appearance of the cells of the second type as prescribed in zone (e′). The nucleus in those containing little myelin is often unchanged, as the amount of substance increases the nucleus tends to become more and more diffusely staining and irregular in outline; it may become quite pyknotic.

Finally, the section terminates in a border of thickened pia (h). Its capillaries are somewhat enlarged. Polymorphs are not observed. There is no obvious cellular infiltration. Immediately under the pia is a narrow, incomplete layer in which degeneration appears to be more active than further in, and unphagocyted myelin droplets of small size are seen.

Taken as a whole, the section is conspicuous in the unusual development and sharp definition of the fibrous capsule, or zone of connective tissue reaction, and in the prominence and great variety of the "cerebral granule cells," of "Gluge's corpuscles."[3]

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3. Gluge, Gottlieb: Abhandl. f. Physiol. u. Pathol., Jena, 1841, pp. 30 and 35, and Plate I.

DISCUSSION

Neither the clinical history nor the necropsy findings, gross and microscopical, throw any certain light on the etiology of the condition found postmortem. It is necessary to fall back in part on a consideration of the etiological possibilities. Of these, three stand out prominently, and may be taken up in inverse order of probability: glioma, solitary tubercle and pyogenic abscess. A fourth and more remote possibility may be mentioned in passing—cerebral cysts.

Cerebral cysts in children may be the result of one of several conditions. Necrotic cysts may replace areas of softening. Cyst formation may follow hemorrhage[4]—porencephalic cysts are probably to be included here. Cysts appear also in connection with gliomas. Those due to cysticercus and echinococcus do not appear to have been observed in children; their contents are also distinctive.

The content of such cysts is usually a clear or milky fluid, the opaqueness being due to the presence of numerous fat-containing cells (Ziehen).[5] No reference is found to the appearance of puriform contents unless infection has occurred. The wall of the cyst may or may not be pigmented.

That such a condition was here present seems a most remote possibility.

Glioma.—After solitary tubercles, gliomas are the most common cerebral tumors of childhood. They, too, may form cystic cavities containing puriform material (Ziegler).[6] They may be highly vascular. Where hemorrhage or softening occurs, there appears, says Ziegler, a cavity filled with cloudy white or brown, more or less liquefied masses. Sometimes the glioma tissue forms the wall of a cyst which contains clear serum. The literature at hand does not show how frequently the condition may simulate abscess.

Solitary Tubercles.—These are, in comparison with abscess, very common in childhood. Tuberculous tumors are the most frequent form of intracranial neoplasm in childhood; over 50 per cent. of all brain

4. In adults, the tissue adjacent to an area of hemorrhage responds in the course of two months with the formation of a capsule composed partly of connective tissue derived from the wall of the blood vessels and partly, according to Ziehen (in Bruns-Cramer-Ziehen Handbuch der Nervenkrankheiten im Kindesalter, Berlin, 1912), of glia. Gluge's cells appear in the neighborhood; the injured tissue undergoes colliquative necrosis (Ziegler: Lehrbuch der pathologische Anatomie, Jena, 1906) and is removed or absorbed; the color of the contents passes gradually through browns into yellows, and ultimately becomes milky or quite clear. This last is, as a rule, the definitive condition in children (Ziehen) though in adults scar formation seems to be more common.

5. Ziehen: In Bruns-Cramer-Ziehen Handbuch der Nervenkrankheiten im Kindesalter, Berlin, 1912.

6. Ziegler: Lehrbuch der Pathologische Anatomie, Jena, 1906.

growths in childhood are of this type (Starr).[7] They sometimes suppurate and break down, and may then simulate simple abscess. Ziegler wrote:

> Not infrequently softening and liquefying processes appear in the tubercle and lead to the formation of abscess cavities filled with yellowish-white pus, or, indeed, with greenish-white pus.

Ziehen considered the existence of idiopathic abscesses in children highly doubtful, and mentioned solitary tubercles that have undergone suppuration as a possible explanation of some cases of so-called idiopathic abscess. In isolated cases, tubercle bacilli have been demonstrated in the wall and contents of the cavity (Fraenkel,[8] 1887, Oppenheim[9] and others,[10]) but in the main, the recognition of the tuberculous origin of such abscesses must be extremely difficult.

Pyogenic Abscess.—Pyogenic abscesses of the brain are quite rare in children. They are decidedly rarer than solitary tubercles and other tumors, and are exceptionally rare under 5 years of age. In a collection of 223 cases of cerebral abscess, Gowers found 10.7 per cent. occurred in patients under 10 years of age. Okada,[11] in 141 cases of cerebral abscess, found 11.6 per cent. occurred in the first decade, and 38.3 and 30.8 per cent., respectively, in the next two decades.

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7. Starr: Organic and Functional Nervous Diseases, New York and Philadelphia, 1913, Ed. 4.

8. Fraenkel, A.: Ueber den tuberculösen Hirnabscess, Deutsch. med. Wchnschr., 1887, xiii, 373. Fraenkel's case was that of a young mechanic. An abscess cavity the size of a hen's egg was found in the left hemisphere at necropsy. It possessed a firm membranous wall 2 to 3 mm. in thickness. The adjacent brain tissue was soft, edematous, and yellowish-white. Neither in the brain nor elsewhere in the body were any gross tubercles or caseous areas found. The content of the cavity was purulent and without caseous particles. To the naked eye it had an appearance throughout of ordinary (connective-tissue) pus, homogeneous, odorless, somewhat thick or creamy. On microscopical examination none of the ordinary pyogenic organisms were found. Instead of these, innumerable tubercle bacilli were found, both in pus and in the membranous wall of the cavity. No microscopic tubercles were present.

9. Oppenheim: Lehrbuch der Nervenkrankheiten, Berlin, 1913.

10. Roger's frequently quoted report (Abcès Cérébraux Multiple, etc., Rev. neurol., 1909, xvii, 772) is of interest here. He recorded a case of multiple tuberculous abscesses in the brain of a woman of 39, in whom there were tuberculous pulmonary foci, but who came under observation because of hemiplegia. He reviewed the literature of the subject and found that the cerebral abscesses of the tuberculous contain a creamy thick pus of greenish-yellow color, in every way similar to the pus of the other abscesses. Also that the wall of the abscess shows nothing distinctive; even in the cases in which acid-fast bacilli are present, the wall does not contain giant cells. He thinks the tubercle bacillus acquires under certain conditions the property of forming frankly pyogenic pus. His own case, however, showed a few diplococci in the pus.

11. Okada, W.: Diagnose und Chirurgie des otogenen Kleinhirnabscess, Klinische Vorträge a. d. Geb. d. Otologie u. Pharyngo-Rhinolgie, Jena, 1900, p. 311.

Okada's figures also showed that cerebellar abscesses occur about one half as often as cerebral abscesses during the first ten years of life. (It had previously been thought that the ratio was nearer one to four.) He found two cases under 4 years of age (2 and 3 years, respectively), and four cases at 4 years of age.

In contrast to the above figures, Heiman,[12] in 535 cases of ototic brain abscesses, found only 3, or 1 per cent., in children under 5 years of age, and but an equal number in the next decade.

The two great causes of pyogenic abscess are middle-ear diseases and trauma. The former is considered much the more common. Hegener[13] found 0.5 per cent. of 5,000 patients with chronic inflammation of the ear, seen at the Heidelberg clinic (1897-1906), developed abscesses of the brain. Three quarters of them were cerebral abscesses. Heiman collected 640 cases of otitic abscesses from the literature and found almost one quarter followed acute inflammation of the ear; and Dench[14] found twenty out of one hundred cases followed acute otitis.

These abscesses are solitary in 80 to 85 per cent. of the cases. Metastatic or embolic abscesses are usually multiple and are even rarer in children than are solitary abscesses. Seventy-five per cent. of these solitary abscesses of childhood occur in the white matter of the hemisphere, being relatively more common in this location in children than in adults (B. Körner[15]). The remaining 25 per cent. appear in the cerebellum.

Trauma is a less frequent cause of solitary abscess, though second in importance. Considering all ages, Gowers found 24 per cent. were due to trauma. Abscess formation may follow even simple concussion. It usually occurs in the neighborhood of the injury, but may be produced by *contre-coup*. These abscesses of traumatic origin are usually solitary. Infection of the injured areas may occur long after the infliction of the injury, abscess appearing as a late result even ten or twenty years after the time of injury. The symptoms usually appear, however, in the first two weeks.

In the present case, there is a history of neither trauma nor middle-ear disease, and no findings suggestive of either were made at necropsy.

Thrombosis and embolism are possible causes of cerebral softening and subsequent abscess formation in children, but need only be men-

12. Heiman: Ein Fall von akutem otitischen Schläfenlappenabscess, Arch. f. Ohrenh., 1905, lxvi.

13. Hegener: Labyrinthitis und Hirnabscess, Beitr. z. Anat. u. Physiol., Path. u. Therap. d. Ohres, etc., Berlin, 1909, ii, 359; Statistik der Ohreiterungen und Hirnkomplikationen, etc., Ztschr. f. Ohrenh., 1908, lvi, 3.

14. Dench, E. B.: Otitic Brain Abscess, Am. Jour. Med. Sc., 1907, New Series, cxxxiv, 692.

15. Körner, B.: Citations from Ziehen and from Okada (see Notes 5 and 11).

tioned here. Metastatic abscesses are usually multiple. Thrush has been noted as a case of cerebral abscess by Wagner, Holt,[16] Zenker and Ribbert, Aschoff[17] and Ziehen.[5] In Wagner's case, the abscesses were multiple and the same fungus was obtained from the abscesses as from the mouth. Actinomyces and streptothrix as causes of cerebral abscess do not appear to have been found in children.

The pus found in pyogenic abscesses is variously described as being thick, greenish-yellow and sometimes fetid; characteristically greenish and thin; thin or cheesy; creamy or thin, grayish-red or stringy, usually acid, often green, or (from the presence of iron sulphid) blackish-green and often slimy gray; while according to Ziegler it is usually creamy, yellowish white or lightly greenish tinted.[18]

Whatsoever their cause, solitary abscesses in children as young as this are extremely rare.

Granule Cells.—A few words may be said about the granule cells of the central nervous system, since they form such a prominent feature in this case.

They were first described by Gluge[3] in 1841, and have long been called "Gluge's cells." They are more commonly called simply "granule cells," or "granule cells of the central nervous system." Our knowledge of them has been recently reviewed in its historical development by Ciaccio.[19]

Their origin has been a matter of dispute almost since their discovery. New methods of neurological technic and study have lent their support in turn to this view and to that, without confirming any. The pictures usually seen in pathological specimens have proved too complex for unraveling, and there remains very much that is yet obscure. That the granule cells are not derived from the nerve cells is certain. They are derived either from the supporting cells of the central nervous system, the neuroglia, or they are derived from the mesenchymal cells that have come in with the capillaries, the adventitial cells, for example.

The problem is being attacked in its simpler forms from the experimental side. Tanaka[20] has shown recently that, in the case of small

16. Holt: The Diseases of Infancy and Childhood, New York, 1911.

17. Aschoff: Pathologische Anatomie, Jena, 1911.

18. Where statements incorporated in the above discussion are not derived from standard textbooks, such as Adami (Adami and McCrae: A Textbook of Pathology, Phila. and New York, 1914), Ziegler,[6] Aschoff,[17] Delafield and Prudden (Pathological Anatomy and Histology, New York, 1909), their source is indicated.

19. Ciaccio, C.: Beitrag zur Kenntnis sogenannten Körnschenzellen des Zentralnervensystem, Ziegler's Beitr. z. path. Anat. u. allg. Path., 1911, l.

20. Tanaka, Takehiko: Experimentelle Untersuchungen über die Herkunft der Körnchenzellen des Zentralnervensystems, etc., Ziegler's Bietr. g. path. Anat. u. allg. Path., 1911, l.

uninfected cortical wounds the granule cells are derived almost entirely from the preexisting glia cells, if not, indeed, entirely from them.

With a *cold* glass probe, or needle, he produced aseptically slight wounds in the cortexes of a series of guinea-pigs. He found on killing the animals at intervals after operation that the polymorphonuclear cells and mononuclear cells were present in numbers only up to the fourth day, and very rarely thereafter. The polymorphonuclear cells may take up degeneration products and stain the size of true "granule cells," but they have always multiform, lobulated, nuclei, and may be excluded as a source of true granule cells. The lymphocytes are extremely few in number as compared with the granule cells, after the fourth day, and they remain small. In few cases, Tanaka saw a few granule cells of small size that were apparently derived from lymphocytes, but the nucleus of the majority of the granule cells was larger and paler and the chromatin differently disposed within it. Proliferation of the adventitial cells of the neighboring blood vessels was very infrequent and granule cells were rarely found in such close proximity as to suggest derivation from adventitial cells. Such origin cannot be excluded, but must be regarded as relatively quite unimportant. This is also true of the fixed tissue cells; the author could find no transition forms from fibroblast to "granule cells."

The great bulk of the "granule cells," according to Tanaka, are derived from the glia cells.

On the third day after injury (of the kind described) signs of mitoses and definite increase in the number of these cells may be seen. There is evidence of reaction in the enlarged nuclei and the increased protoplasm, which is laden already with a few granules of detritus. By the seventh day the increase in the glia cells is marked, and some possess several nuclei. Intermingled among the hypertrophied glia cells are true granule cells. The nuclei of these show the greatest resemblance to those of the adjacent hypertrophied glia cells, and every transition between the two types of cells may be seen.

In their development into "granule cells" the glia cells seem to become detached, says Tanaka, from their fibers and to become ameboid in character.[21]

The transition into granule cells occurs predominately (under the conditions of the experiment) during the first ten days. After two weeks the nuclei have already become smaller, are for the most part

21. That such independence should exist between the glia cell body and the fully formed glia fiber is compatible with the views of Weigert (Beitr. z. Kenntnis d. n. mensch. Neuroglia, etc., 1896), though disputed by Held (Ueber den Bau d. Neuroglia, etc., 1904). (Citations from Tanaka.[20])

angular, and stain more deeply. The cells slowly vanish in situ, or are carried off into the lymph spaces.

Tanaka saw no evidence of transformation of "granule cells" into cells of other types. Scar tissue developing from the overlying pia in time filled the defect caused by the injury in this experiment; in the deeper layers the neuroglia contributed to the scar formation.

This work is unconfirmed as yet. Ciaccio's[19] studies led him to quite other conclusions. He decided that stainable lipoid globules may be found in (a) many degenerating cells in the central nervous system (and other tissues), and in (b) a special type of phagocytic cell, the "interstitial lipoid cell." This interstitial lipoid cell is derived, he says, from the mesenchyma, by way of the adventitial cells of the blood vessels near the injured area.

In the case here presented the microscopical pictures support Tanaka's view of the origin of the granule cells, rather than the older views. In the least injured tissue, for example in zone (g), the neuroglia cells are least affected, occasional well-defined granule cells are seen, and numerous less differentiated intermediate forms. There is, in this zone, no demonstrable reaction on the part of the capillaries. As the tumor is approached and the zone of greater compression and degeneration is entered (e'), the neuroglia cells, the granule cells, and the transitional cells become much more numerous. Reaction on the part of the capillaries, however, becomes apparent only later.

In view of the absence of signs of reaction on the part of the capillaries in zone (g) and in the absence of any demonstrable infiltration by cells derived from the blood stream itself, it is difficult to believe that those cells that appear to be undifferentiated neuroglia cells and similar cells containing minute globules of stainable lipoids, and finally, fully differentiated granule cells, are not all derived from preexisting cells of the central nervous system—the neuroglia. To postulate the presence of some undifferentiated mesenchymal cell, deposited in the brain tissue at some time during development and now reacting to stimulus, seems unnecessary.

SUMMARY

The case here reported represents a rare condition; multiple large abscesses in the hemisphere of an infant under 2 years of age.

It ran its course under the picture of chronic internal hydrocephalus.

That chronic internal hydrocephalus of the communicating type was not present was shown clinically by the phenolsulphonepthalein test.

The condition found at necropsy resembled closely that of multiple pyogenic abscesses of the left hemisphere.

It was not possible, however, wholly to exclude multiple tubercles which had undergone puriform softening.

Microscopically, the case is noteworthy in the unusual number of Gluge's corpuscles that are present, and in relation to theories of the origin of these cells.

I wish to thank Dr. Howland for the privilege of reporting this case, and Dr. Adolph Meyer for his personal interest in the study of the brain in the Neurological Laboratory of the Henry Phipps Psychiatric Institute.

Severn Apartments.

STUDIES ON THE PINEAL GLAND

I. EXPERIMENTAL OBSERVATIONS *

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INTRODUCTORY

The ancients believed that the pineal body or cornarium, as it was called, regulated the flow of vital spirits from the brain to the spinal cord, acting in this capacity in a manner similar to the pylorus of the stomach. It was assumed that it was a part of the brain, capable of movement, and stood as a guard between the third and fourth ventricles. But it is remarkable to find in the works of Galen,[10] whose name still clings to the neighboring veins, that he used the term "acervulus" in describing the psammona or sand bodies found in the gland, and in his works recur such illuminating statements as the following: "The pineal was devised for the same purpose as the other glands of the body." In the first place, "it is in substance glandular," and, observing that the blood supply came from the same source as that of the choroid, he felt that it must be as distinct from the brain proper as is this latter structure. Again, "if it was a small part of the cerebrum itself it would be found . . . at times moved from its own situation by compressions," and lastly, he lays stress on the fact that it is not a part of the brain, because "it clings to it from the outside." From the second century until the time of Faivre, the Galenic ideas concerning the structure and function of this body prevailed, though, as is well known, Descartes regarded it as the seat of the soul.

The careful comparative studies of this organ by Faivre[7] in 1854 form the basis of all subsequent anatomical researches. For the next fifty years the investigation of the pineal was confined to its embryology, anatomy, and its pathology in relation to the few recorded clinical cases of tumor. During the last fifteen years only, have attempts been made to study the function of the gland by the use of the present-day experimental methods.

Because of our newly acquired knowledge that the pineal body undergoes a normal, physiological atrophy at the time of puberty, as well as the fact that several cases of tumor of the gland occurring before puberty have been associated with a marked precocity in the realm of both primary and secondary sexual characteristics, it would seem

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plausible to assume that the gland, when physiologically active, tends to inhibit the development of the sexual function.

Experimentally, this problem has been attacked in the usual two ways, namely, by extirpating the gland, and by the oral administration of its substance. As to the former method, the experiments, notably those recently carried out by Foà,[36] support the assumption just alluded to, he having experimentally reproduced by removal of the pineal body in chickens the syndrome termed by Sarteschi "macrogenitosomia precox."[39] Our own observations, to be recorded in this paper, also are interpreted in support of such a view. On the other hand, the feeding experiments of Dana and Berkeley,[42] and McCord[46] seem to indicate, contrary to what would be expected, that prolonged administration of the glandular substance likewise hastens rather than retards the somatic and sexual development.

It will be seen, therefore, that the subject needs further investigation, but before recording such results as have been obtained in this laboratory, some review is necessary, as much has been added to our knowledge since the résumé in 1909 by Marburg[54] and in 1912 by Kidd.[50]

Past Embryological Findings

Practically all recent investigators support the view that the gland is derived from a separate and distinct evagination of the roof of the third ventricle. Edinger[5] is apparently the first author to uphold the unpaired origin of the pineal gland, former investigators (Gaskell,[11] and Dendy[3]) having brought rather meager evidence to show that the buds forming the two pineal organs in lower vertebrates were not both in the median line. Studnicka,[21] in his comparative embryological studies, finds that there are always two midline evaginations, the anterior becoming the pineal eye in those forms which retain this structure, and the posterior, the pineal body proper.

Marburg,[54] from studies of human embryological material, also believes in the development of the pineal body from a separate outgrowth, the pineal eye being no longer demonstrable in man. He gives a schematic representation of the relationships of the four evaginations of the diencephalon in the pineal region. Of these diverticula, the pineal body proper is concerned only with the most posterior, while the others, in the lower vertebrates, develop eventually into (1) the paraphysis, (2) the dorsal sac, and (3) the pineal eye.

Warren,[23] through studies of *Reptilia,* also supports the view of development from a single bud. He concludes that the pineal eye and the epiphysis of the lizard arise as two outgrowths from the epiphyseal arch, that for the eye being immediately in front of that for the epiphysis. This bud first appears in the second embryonal month

(Marburg, Schüller, et al.). In reptiles, birds, and mammals, the pineal process consists first of a row of follicles that are empty, and later these become filled with nucleated cells (Münzer).[51]

According to Studnicka, the pineal body is present in all vertebrates with the exception of *Myxinoids* and *Torpedo marmorata*. D'Erchia,[6] however, finds it lacking in *Torpedo occelata;* and other authors say that it is not present in *Crocodilia*.

Past Anatomical Findings

In man, the body lies just beneath the splenium of the corpus callosum, resting on the superior colliculi of the corpora quadrigemina. It is about 1 cm. in length and half as broad as it is long. Its shape may be roughly described as resembling that of a pear or a cone. In other species, its size varies more or less directly with the size of the animal, although relatively larger in the rabbit and guinea-pig than in the cat and dog. Its situation also in animals such as the guinea-pig, rabbit, and in birds is more superficial, owing to the relatively much greater development of the corpora quadrigemina in them, and the relative thinness of the occipital lobes of the cerebrum. The vena magna Galeni accompanies the gland throughout its entire extent, and in the chicken (Foà) and also the guinea-pig and rabbit, the separation of these two structures in an operation for extirpation is impossible.

The pineal is surrounded by a thin capsule of connective tissue, which continues anteriorly as far as the so-called *Schaltstück*, by which the body forms its connection with the taenia habenularum. This capsule was recognized and described by Faivre, and he also described the "globular parenchyma" and "acervulus or sand." Over the *Schaltstück*, which is not a true stalk but an attenuated portion of the anterior end of the body, the covering is ependyma, according to Marburg, whose monograph should be consulted for the finer structure and relation of the taenia to this portion of the pineal.

From the capsule, thin strands of connective tissue penetrate the interior of the gland, forming a meshwork of irregular lobules or follicles in which lie the other elements constituting its structure. The blood vessels accompany these fibrous traberculae. The lobulation is most evident and most regular in man and the larger animals (calf, sheep), but in the guinea-pig the connective tissue framework is very intricate and not very evident, the gland at first sight appearing to be simply a mass of cells held together by the capsule.

The cellular elements are somewhat varied, and differ slightly in different species, but certain types of cell are common to all. First, there is what may be called the parenchymal cell, or pineal cell proper; a cell whose outline is irregular and hard to make out, owing to its poorly staining cytoplasm. The nucleus is round and stains intensely

with hematoxylin, as does also the nucleolus. The nucleus, in addition, contains many fine granules, on which is based the anatomical belief of the glandular nature of the organ. This glandular nature of the parenchymal cells is brought out by nearly all anatomical observers, being especially marked in birds, according to Sarteschi. Dimitrova,[4] Studnicka, Krabbe[15] and Marburg comment at length on the granules of the nuclei. In a recent contribution, Krabbe also lays stress on the extrusion from the nuclei of pyroneutrophil granules.

Next to the true parenchymal cells, in point of number, come the glial cells. These form a constant and numerous element in all glands which have been studied by the various investigators, from Köllicker[14] in 1850 to those of the present day. For a more detailed account of the structure of these cells, reference may be had to the works, among others, of Dimitrova, Studnicka, Krabbe,[15] Sarteschi[19] and Marburg. In the calf particularly and in the sheep, there seem to be two zones of glial cells, an anterior, in which the cells are of a larger type, and a posterior in which they are definitely smaller and more numerous.

Among other important structures found in the pineal of certain species (ox, calf, sheep, dog) are the cavities resembling thyroid vesicles (Dimitrova) from which may arise the cysts which have been described by Jordan,[13] Marburg and others.

The so-called sand bodies are another constant and characteristic finding, especially in the pineal of man and the larger animals. Other structures which have been said to occur are sympathetic nerve cells (Cajal,[2] Retzius[16]), cells resembling the latter (Dimitrova), calcifications and lipoid substances (Krabbe), striated muscle fibers (Dimitrova), ganglion cells (Studnicka), and possibly mitochondria (Biondi[1]).

Studies of the paths of secretion of the pineal have been made by Loewy.[29] He injected dye stuffs into its substance, and thus demonstrated three types of spaces: (1) pericellular, (2) interlobular, and (3) spaces connecting the gland substance with extraglandular structures (choroid).

Physiological Observations

I. Administration of Extracts

(*a*). *Acute Effects.*—A limited number of physiological experiments with extracts of the pineal have been reported, and these have, in the main, been negative so far as any striking effect on the bodily activities is concerned.

In 1898 Howell[27] made brief mention of some intravenous injections of pineal extract, in which the effect on the blood pressure was inconstant. Von Cyon[25] in 1903 injected intravenously extracts of the pineals of the ox and sheep. Small doses were said to have no effect

on the blood pressure, but gave a slight tachycardia. In larger doses a slowing of the heart was noted, together with a frequent pulsus bigeminus or pulsus trigeminus; and a fall in blood pressure sometimes occurred. He, moreover, was led to revive the ancient view of a mechanical function which regulates the flow of cerebrospinal fluid from the third ventricle, because of changes observed in its form after electric stimulation. Krabbe[15] also supports this older theory in a recent discussion of the function of the pineal.

Dixon and Halliburton[20] in 1909 studied the effects of extracts of the pineal bodies of sheep, but fail to say whether the material came from adult or from young animals. The results were relatively negative on blood pressure, heart rate, and respiration, as well as on the volume of the intestine and kidney and on the rate of kidney secretion.

The studies of Jordan and Eyster[28] in 1911 are also negative with regard to any great effect on blood pressure. A relatively slight fall was recorded, together with an intestinal vasodilation, and a transitory diuresis with glucosuria was observed in 80 per cent. of the cases.

In 1912 Ott and Scott[31] found the effect of pineal extract on arterial tension, urinary secretion, glucosuria, intestinal and uterine contractions, and pupillary dilatation to be practically negligible. An insignificant vasodilatation of the kidneys was recorded, together with a little increase in the flow of urine.

Personal Observations of Acute Effects.—With the idea that extracts of very young animals might be more potent than those commonly employed, a series of observations was made with glands from calves and young sheep. The material was obtained fresh from the abbatoir, ground up in a mortar and dried in the air. A part was mixed with lactose in the proportions of 1:3, and when used was weighed out as powder and dissolved or taken up in normal salt solution. Medium-sized dogs were used and the injections were made into the left external saphenous vein.

Injections of small amounts (0.1 gm.) gave practically no result. There was a variable, moderate fall in blood pressure, with no effect on respiration or on the flow of cerebrospinal fluid. With larger amounts of the powder (0.5 gm.) a constant fall in blood pressure was recorded, varying from 10 to 24 mm. of mercury. The acute effect of the injection lasted on an average about two minutes, the pressure in all cases showing a subsequent gradual rise to normal over a period varying from ten to fifteen minutes. In no case was there a subsequent pressor response.

In order to test the effect on the flow of cerebrospinal fluid, the Cushing-Weed method of puncturing the third ventricle was employed, each drop being recorded as it fell from the cannula by a marker on the drum. The effect on the cerebrospinal fluid was that which might

be expected merely from the concomitant fall in blood pressure, namely, a slowing of the flow, or in some cases an absolute stoppage. The injections made with extracts of the fresh glands before drying, either by boiling or extracting in warm salt solution, were in all essentials similar to those of the dried powder. In order to see whether the effects recorded were due to the pineal extract itself or to the cholin content of the gland, $\frac{1}{300}$ grain atropin was used in a series of injections along with the pineal extract. The results obtained from these injections varied considerably, but in all cases a slight fall was demonstrable, and in at least one case the fall was measurably as great as that caused by an injection of the extract without the atropin fifteen minutes previous.

It was found, therefore, in agreement with our predecessors, that intravenous injections of the extracts of the pineal body of young animals cause a constant but relatively slight fall in blood pressure. The injection causes no increase in the flow of cerebrospinal fluid and the fall of blood pressure, moreover, is not due entirely to the cholin content of the gland.

(*b*). *Prolonged Effects.*—Several investigators have administered pineal substance to animals over long periods, either by the method of feeding the dried gland by mouth or injecting extracts of it intraperitoneally.

Dana and Berkeley[42] in conjunction with Goddard and Cornell carried on a series of such experiments and conclude that the ingestion of powder made from the pineal body hastens the growth of young animals. The animals used were young guinea-pigs, kittens and young rabbits. In all cases the subjects, which were fed the pineal powder, gained a relatively greater amount in body weight than the controls over the various courses of observation, extending from two and one half to five months. The actual figures show that the gain of fed animals over controls varied from 7.5 to 20 per cent.

As a result of these investigations, pineal gland substance was administered to a series of fifty defective children and they felt that it proved of value, though no results were obtained in cases of frank idiocy or gross physical defects. Improvement was noted in cases of simple retarded mental development and mongolism. The controls gained more in body weight, and the subjects more in mental capacity. They could not be certain of any mental defect in children which might be ascribed to hypopinealism or apinealism.

In 1914 McCord[46] studied the results obtained by feeding powdered extract to young guinea-pigs, young chickens and puppies. The extract was made from the pineal glands of "young adult cattle," dried and mixed with lactose. A noticeable overgrowth occurred in body weight of the animals fed with the extract over the controls. His statistics

show a 23 per cent. gain for the guinea-pigs fed with pineal over their controls, and in chickens also he says there was a noticeable increase in size in those fed on the gland substance. He notes further that among the females which received the pineal powder there is a greater tendency to earlier pregnancy than among the controls. His investigation with puppies was unsatisfactory, owing to distemper. In more recent papers[47] he confirms his earlier results. In his later series hypodermic injections of pineal extract were substituted for the oral administration of the gland, and the guinea-pigs so injected showed 26 per cent. gain in weight over controls during the six weeks of observation.

J. B. Boehm, working in this laboratory during the past year, has also studied the effect of prolonged oral administration of pineal gland substance to guinea-pigs and rats. His results were conflicting, in that in some cases the fed animals showed greater development of their genital organs than the controls, while in other cases the controls outstripped the animals to which the pineal was administered.

II. EXPERIMENTAL EXTIRPATIONS

(*a*). *Previous Observations.*—The literature appears to contain but seven references to any attempts at experimental removal of the pineal body. Sarteschi[38] in 1910 reported negative results on a series of eleven rabbits, only two of which lived, and in only one of these was the gland thought to be totally extirpated. In 1913, however, he succeeded in removing the pineal from two puppies and three guinea-pigs.[39] One puppy was said to have gained definitely in weight over its control, and its sexual development accelerated. At necropsy its testes were much larger than those of the control. The other puppy had no control, but its tests were said to be much larger than normal, when it was sacrificed before reaching adult size. As to the guinea-pigs, the author found an increase in weight of body and in the size of the testes in one experimental animal over its control. The testes of the other two guinea-pigs were said to be "well developed" when sacrificed, but there appear to have been no controls. There were no changes in the other glands of internal secretion.

Biedl[48] in 1910 attempted without success to extirpate the pineal in puppies. No changes were noted in the three survivors of his series. The following year Exner and Boese[35] reported negative results in a series of ninety-five young rabbits, of which only six survived to maturity and these showed nothing which could be demonstrated as a departure from normal.

Foà[36] in 1912 reported the only notable changes which up to that time had been recorded after total experimental pinealectomy. He succeeded, with chickens, in having three cocks and twelve hens live to maturity after extirpating the gland. No changes occurred in the hens.

The pinealectomized cocks showed various evidences of hastened maturity. They crowed and gave evidence of sexual instinct from forty-two to seventy-nine days before their controls. There was a marked relative hypertrophy of the combs and testes of the experimental over the control cockerels.

Two years later Foà added some confirmatory results to his earlier work.[37] In a second series two males and five female chickens survived pinealectomy. Again no changes were observed in the case of the females, but the two pinealectomized males showed a much greater increase in the size of their combs and testes than did their controls. The author also attempted to remove the gland in eight young rats, and of the four survivors, three were males. These animals apparently gained in body weight over controls up to a certain length of time after operation, when the weights of both became about equal. One rat showed an increase in the weight of its testes over the control. Microscopically, the testes of pinealectomized animals, both chickens and rats, showed relatively larger canaliculi and tubules than did their controls. No apparent changes occurred in the other glands of internal secretion.

A series of observations on canine pinealectomy were made by Dandy under Dr. Cushing's suggestion in the Hunterian Laboratory in Baltimore in 1912. Some successful extirpations were achieved, but the results were negative. The method has subsequently been perfected by Dandy, who records a series of further experiments with equally negative results.[40] Thus, though Sarteschi's and Foà's experiments with rats are suggestive, no conclusive changes have been observed as yet in mammals.

(*b*). *Personal Observations.*—The topography of the pineal region in young dogs and cats was studied with a view to the most favorable surgical approach, but after numerous operative trials which resulted in incomplete resections, further work on these animals was abandoned. The same experience was had with young rabbits, and although the operative results were slightly better than in the case of the puppies, they were on the whole equally unsatisfactory. The operation was done in one stage, and in a majority of cases the gland was completely extirpated, but no animal survived the inevitable hemorrhage more than forty-eight hours. Even the controls, which were subjected to a simple decompression over the pineal region, usually succumbed within a week.

Guinea-Pig Series

The operative results with these animals, however, were very much more successful, and the complete removal of the gland was accomplished in a large percentage of cases. The animals when operated on varied in age from 2 days to 6 or 7 weeks, and usually the experimental and control animals were members of the same

litter. If at least two males or two females could not be obtained from the same litter, the animals which were chosen for operation were picked from the same breed, and at the start were as nearly as possible equal to each other in weight and age. The difference in weight in such animals was never more than a few grams, and in age never more than two to four days. The two sets of experimental and control animals were kept and fed under identical conditions, the cages of both being of the same size and in the same situation, and the amount of food for each lot was weighed out equally.

On the whole, the animals did very well, considering that they were operated on at so early an age, and if tided over the first forty-eight hours they usually lived until sacrificed, although a few of both experimentals and controls died after the course of several weeks, due to intercurrent causes. In all, 144 pigs were operated on, and of these an attempt was made in 82 to extirpate the gland, while in the remaining 62 a control trepanation was performed. The larger number of experimental animals is due to the fact that the operation on them being more severe, there were more immediate casualties, necessitating a greater number of subjects for operation. Of the 82 experimental animals, 48 lived to maturity or until sacrificed, while of the 62 controls, 42 lived an equal length of time as their experimentals.

In nearly every instance postoperative death was due to hemorrhage from the large vein of Galen. The mortality is necessarily high. Exner and Boese in 1911 quote 75 per cent. of immediate deaths in young rabbits; Sarteschi in his first report shows 72 per cent. deaths with the same species, while in his more recent work his mortality was 87.5 per cent. with guinea-pigs and 80 per cent. with puppies. Foà's percentage of deaths from operation on chicks was 76, but in 1914 he reduced this to 30 per cent., while of the eight young rats mentioned in his last paper, four died, a 50 per cent. rate.

TECHNIC

As perfect asepsis as possible was employed, and no infections developed in the entire series. Ether was the anesthetic used throughout. The skin was prepared by shaving and by applying 70 per cent. alcohol, and a piece of sterile gauze dampened in 1:1,000 mercuric chlorid was placed over the whole animal. A small opening in the gauze was then made over the operative field.

After a median line incision over the posterior end of the skull, the periosteum was scraped back with a blunt knife and a chip taken out of the underlying bone down to the dura with a sharp knife. The area was further enlarged until the superior longitudinal sinus was exposed from about its midpoint to where it joins the two lateral sinuses between the posterior end of the cerebrum and the anterior end of the cerebellum. The greater part of the occipital bone was removed in one piece, so that the pineal region was exposed fully. The superior longitudinal sinus was now ligated in two places anterior to the two lateral sinuses and divided with the dura between the ligatures. The posterior flap of dura thus formed was then retracted, exposing the gland. This was grasped firmly with a "mosquito" clamp and gently pulled

out, sufficient tension being exerted to disengage it from its adherent structures without causing it to break apart itself. The gland was put into 10 per cent. solution of formaldehyd and subsequently sectioned. A good deal of hemorrhage always followed the extraction of the gland, but was usually controlled by the pressure of cotton pledgets taken from hot salt solution. The dural flap was then replaced and the skin sutured. For the controls, a similar operation was performed with ligature of the sinus, but the dura was not opened.

TABLE SHOWING AVERAGE WEIGHTS OF EXPERIMENTAL AND CONTROL ANIMALS AT TIME OF OPERATION AND WHEN SACRIFICED

Pair No.	At Operation			When Sacrificed						
	Age in Days	Body Weight		Age in Days	Body Weight		Testes		Seminal Vesicles	
		Op'd, Gm.	Control, Gm.		Op'd, Gm.	Control, Gm.	Op'd, Mg.	Control, Mg.	Op'd, Mg.	Control, Mg.
1	49	249	237	98	382	355	1,830	1,700	2,210	1,030
2	35	179	246	84	284	296	610	560	430	330
3	35	235	279	84	350	351	1,185	910	1,170	570
4	28	207	195	91	325	340	1,980	730	2,280	1,080
5	14	142	153	63	315	300	1,050	830	910	1,050
6	13	122	117	63	265	240	680	470	630	220
7	14	156	164	56	283	315	850	730	940	420
8	7	120	103	56	222	174	500	400	370	260
9	10	170	158	52	237	211	380	270	220	220
10	7	91	80	49	118	131	160	170	120	120
11	10	129	140	45	148	164	140	170	120	150
12	5	115	85	77	254	215	930	710	390	350
13	7* 10	98	113	77	240	213	920	720	400	340
14	10* 7	145	129	63	200	225	490	480	280	350
15	10* 7	110	109	70	245	261	1,100	1,100	970	500
Total...	..	2,289	2,308	..	3,878	3,800	12,915	9,980	11,450	7,000
Average	..	151.2	153.8	..	258.5	253.3	861.3	665.3	763.3	466.6

* Pinealectomized animal.

After operation, the experimental and control animals were put into separate cages, males and females in each lot being kept together from the start, so that an idea of any differences in time of breeding could be noticed. Each animal was weighed weekly. The age at which the various pairs of experimental and control pigs were sacrificed varied from seven and one half to fourteen weeks in the case of males, but females were often allowed to live a much longer period so as to note

the date of their first parturition. When sacrificed, the animals were chloroformed and the testes and seminal vesicles carefully removed and weighed. These, together with the other endocrine glands, were immediately put into Zenker's solution, and after embedding in paraffin, sections were cut from exactly corresponding parts of each organ. The brain of the experimental animals was also removed, together with the meninges, at the time of necropsy, and serial sections cut through the whole of the pineal region so that any trace of remaining pineal gland could be discovered. In fifteen males and twenty females of the series the gland was thus found to have been totally extirpated. It is, therefore, to these animals, with their controls, that the record of our results is confined.

Results (males): Taken as a whole, very little difference was noted in the body weights of the experimental and control animals. As will be seen by the accompanying table, the average weight of

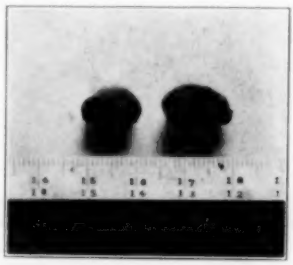

Fig. 1.—Showing testes of guinea-pigs (Pair 1) aged 14 weeks, seven weeks after operation. Right: pinealectomized animal. (Slightly reduced.)

experimentals at the time of operation was slightly less than that of the controls, and when sacrificed from the fourth to the seventh week after operation there was a slight gain in favor of the pinealectomized animals, but both figures are possibly within the normal limits of variation. Both Foà and Sarteschi, however, record a gain in weight of pinealectomized over control animals, so our findings, though not striking, accord with theirs.

In regard to the growth of the genital organs, a much more noticeable increase took place in favor of the pinealectomized animals. As shown by the table, the total weight of the testes of the experimental animals was 12,815 mg. against 9,950 mg. total for the controls. This makes an average of 854.3 mg. for each experimental pig against a 663.3 mg. average for each control. This difference will be seen in the photographs of several of the various pairs of testes of experimental and control animals (Figs. 1, 2, 3 and 4).

It will be noted in the table also that the experimental pigs showed a marked increase in the size of the seminal vesicles over those of the controls. No mention appears to have been made by other investigators

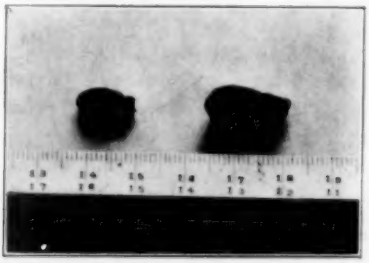

Fig. 2.—Showing testes of guinea-pigs (Pair 4) aged 13 weeks, seven and a half weeks after operation. Right: pinealectomized animal. (Slightly reduced.)

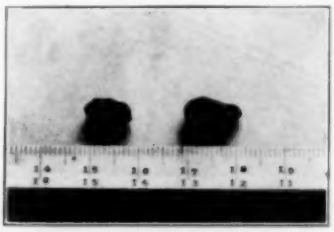

Fig. 3.—Showing testes of guinea-pigs (Pair 6) aged 9 weeks, fifty days after operation. Right: pinealectomized animal. (Slightly reduced.)

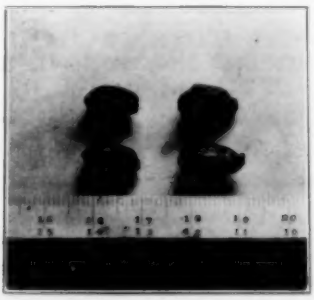

Fig. 4.—Showing testes of guinea-pigs (Pair 12) aged 11 weeks, seventy-two days after operation. Right: pinealectomized animal. (Slightly reduced.)

concerning these organs, which in the case of the pituitary studies made by Goetsch[43] in this laboratory were found so greatly enlarged. Our pinealectomized animals showed a total weight of the seminal vesicles

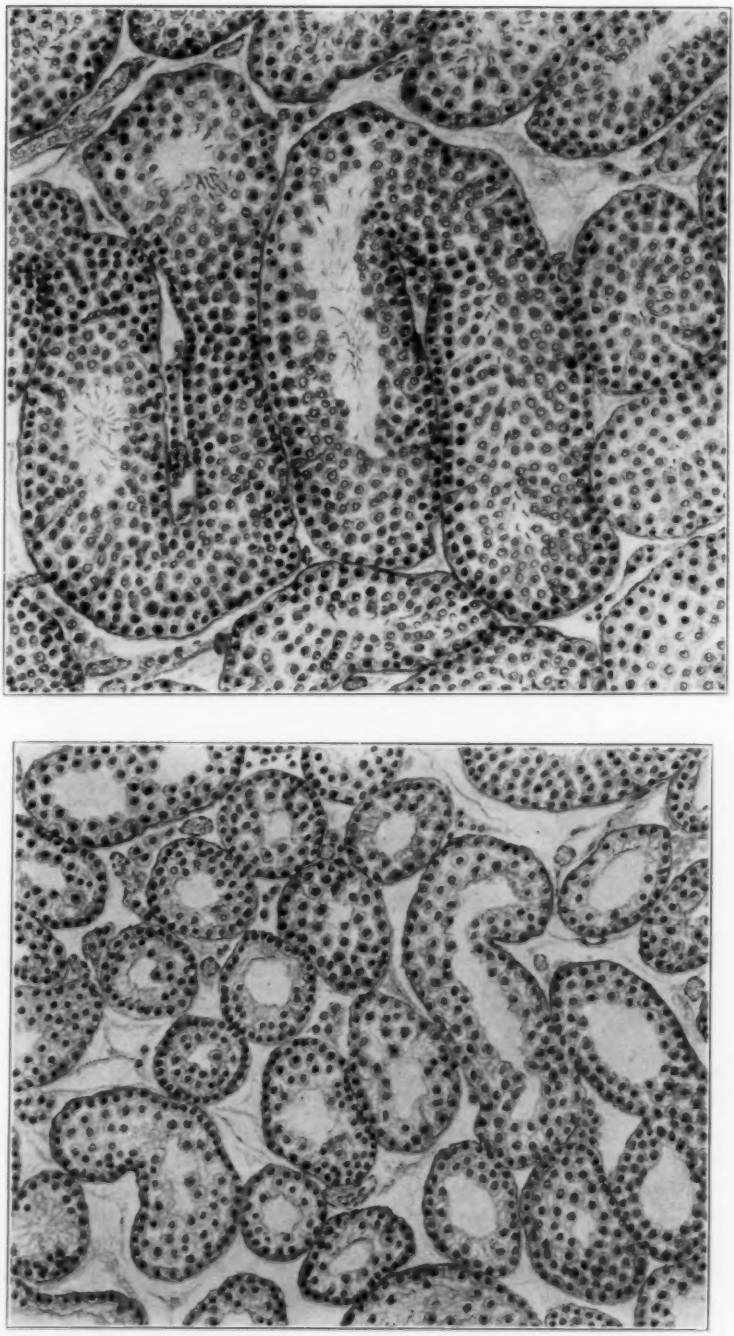

Fig. 5.—Sections through corresponding portions of testes of guinea-pigs (Pair 4) aged 13 weeks. Note large size of tubules with many layers of spermatogenic cells and tails of spermatozoa in pinealectomized animal (upper drawing). (× 100.)

of 11,450 mg. against the controls' 7,000 mg., or an average of 763.3 mg. for the former against 466.6 mg. for the latter. Again, the photograph serves to emphasize the difference which the scales record.

Microscopically, the differences in the testes of the experimental and control animals were perhaps not so marked as might be expected from a comparison of their gross size and weight. Nevertheless, in this respect also, there were changes which indicate a hastened development of the organs under consideration (Fig. 5). The most marked differences occurred in pigs which were sacrificed between the ages of

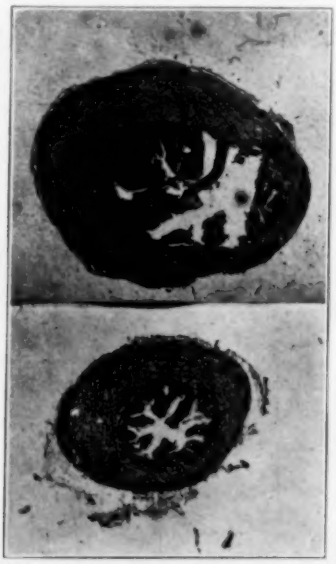

Fig. 6.—Sections through corresponding portions of seminal vesicles of guinea-pigs (Pair 8) aged 8 weeks. Note larger size and more advanced state of epithelial lining of lumen in pinealectomized animal (upper photo). (× 25.)

9 and 11 weeks. If sacrificed before this age, practically no microscopical differences could be detected, while later than eleven weeks the difference again became very slight owing to the proximity of normal maturity.

When taken during the age of maximum difference, the testes of pinealectomized animals show relatively large tubules, their lumina almost entirely filled with the many layers of spermatogenic cells in all stages of growth. Active spermatogenesis is evident. Interstitial cells are abundant, but cannot be distinguished in size or in amount from those of the controls. The tubules of the controls are definitely smaller,

when exactly similar portions of the testes of each are studied, and the layers of spermatogenic cells in the lumina are fewer by far than is the case with the experimental animals. Occasionally there are a few mature spermatozoa, but these are rare, and there is much less uniformity of development, portions of the testis showing tubules in a very immature stage without even a beginning spermatogenesis.

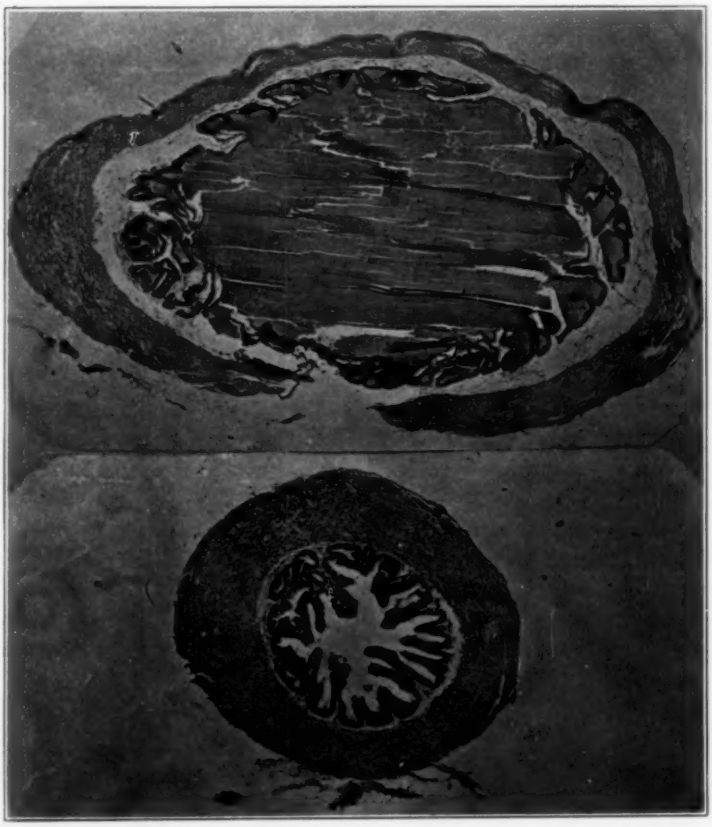

Fig. 7.—Sections through corresponding portions of seminal vesicles of guinea-pigs (Pair 6) aged 9 weeks. Note larger size and thinning of walls due to collection of secretion in lumen in pinealectomized animal (upper photo). Control shows small size and thick walls of immature vesicle, and no evidence of secretion from epithelial lining. (× 25.)

The microscopic picture in the seminal vesicles of the two sets of animals was far more striking than that of the testes. Here no particular age of maximum difference could be identified, except that, earlier

than 8 weeks of age, the vesicle always appeared immature in the case of both. Beyond this age there was a rapid change in the experimental animals, manifested by an enlargement of the lumen of the vesicles at the expense of the thickness of their walls. The cells of the lining mucous membrane were seen to increase in height, while in most cases there was an abundant secretion of colloid material completely filling the lumen. The difference between this picture and that of controls is clearly shown in Figures 6 and 7. Here the cross section of the vesicle, always taken at a corresponding point to that of the experimental, is noticeably less, the walls are thicker and the lumen smaller, as in the immature type. That the lining cells have not yet begun to secrete is evident from the total lack of colloid secretion in the lumen.

Results (females): In accordance with the observations of other investigators, no differences could be made out in size or weight of the female genital organs, nor was there a demonstrable difference when these tissues were studied under the microscope. In regard to body weight, it may be said of them that a similar curve was shown as in the case of males, excluding the ones which became pregnant, as here, naturally, a normal rapid increase was evident.

As to physiological evidence of hastened maturity in females, the incidence and termination of pregnancy is the only factor which we can quote, and here our figures are inconclusive, owing to the fact that in most cases the males were sacrificed before the age of full sexual maturity was reached.

Of the twenty females in which total pinealectomy was shown to have been accomplished, three became pregnant, while out of the same number of controls there were but two. All three experimental pigs were delivered of their young ten days or more before either of their controls gave birth, the earliest of the experimentals being delivered three weeks before either control. When it is considered that the normal period for guinea-pigs to reach sexual maturity is about nine weeks, it will be seen that, in the above instances at least, this period was shortened one sixth to one third.

From the experiences with young guinea-pigs several difficulties were obvious. First, the litters being very small—usually not more than two—it was hard to get a large series with absolute controls. Second, as the time between the birth of guinea-pigs and their arrival at normal maturity is quite short, there was little time to observe the changes which might develop due to the influence of the pineal. Lastly, the relatively long, thin pineal gland of guinea-pigs made complete extirpation very difficult because of its tendency to break when traction was exerted on it.

Rat Series

For the above reasons, a series of operations on young rats was undertaken, and although an epidemic ruined nearly all of the experiments, it was immediately evident that, excluding such an unforeseen factor, these animals on the whole made the more ideal subjects for pineal experimentation. Litters are large and the interval between birth and sexual maturity is far longer than in guinea-pigs. The pineal gland itself is much shorter and less fragile, and can be picked out easily and surely with a pair of small forceps.

As previously mentioned, an epidemic broke out among the cages of rats, and in order to get a fresh start after thorough disinfection, the few survivors were sacrificed earlier than had been intended. Among these, only one or two showed any changes which might be attributed to disturbance in pineal secretion.

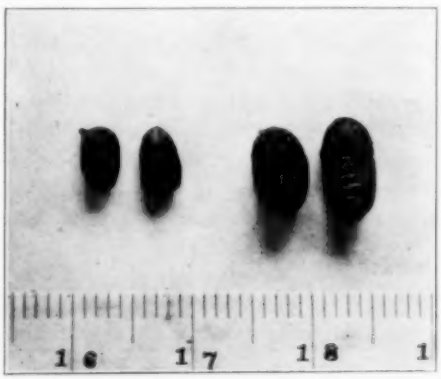

Fig. 8.—Showing testes of rats (Litter 13) aged 9 weeks, four weeks after operation. Right: pinealectomized animal. (×2.)

Two males of Litter 13 were sacrificed at the age of 9 weeks. Complete pinealectomy had been performed on one, and a control operation on the other a month previously. Their sizes and weights at the time of operation were almost identical. When sacrificed, the pinealectomized animal weighed 37 gm., as against 28 gm. for the control. The testes of the former were also much larger than those of the latter, weighing 410 mg. to 250 mg. for the control (Fig. 8).

Two males of Litter 12, a pinealectomized and a control, showed no differences at the age of 9 weeks, these animals also having been operated on a month before. The testes of each weighed 300 mg.

Three males of Litter 22 also showed very slight differences. They were sacrificed when 7 weeks old, their operations having been performed only two weeks previously. Of the three, the pinealectomized

weighed 36 gm. when sacrificed, as against 35 gm. and 31 gm., respectively, for the two controls. The testes of the experimental rat weighed 280 mg., while those of the controls weighed 260 mg. and 280 mg., respectively.

In Litter 23 there was but one survivor, a pinealectomized male, and this animal, although sacrificed when 6 weeks old and only two weeks after operation, showed an increase in body weight from 23 gm. to 31 gm., and its testes weighed 410 mg. Another single, male, pinealectomized survivor occurred in Litter 17. This animal was sacrificed at the age of 9½ weeks, or three and one half weeks after operation. Its body weight was 29 gm. and that of its testes 280 mg. Interesting comparisons with these last two cases, although not actual controls, are the two surviving members of Litter 11. Both these animals had a control operation performed at the age of 5 weeks, and were sacrificed when 9 weeks old. Their weights were 25 and 40 gm., respectively, while the testes of the one weighed 280 mg. and of the other 300 mg.

Aside from the demonstration of the comparative ease of the operation, which will make this species the most desirable for future studies, the results for our immediate purposes are inconclusive. Can the changes which have been observed in these experiments be attributed to the loss of the pineal gland, or may they be attributed to some other injury of glandular or nervous tissue? The only other intracranial organ which is known to influence bodily growth and sexual development is the pituitary body, and it is conceivable that, as a result of the operation which has been described, some secondary changes might occur in that structure, due, possibly, to a postoperative hydrocephalus scar formation, but such a condition has never been observed and, furthermore, it would have led to changes the reverse of those we have seen, namely, to skeletal undergrowth and delayed sexual development. In our series of guinea-pigs the pituitary was studied microscopically and no departure from the normal was noted.

Conclusions

1. Total experimental pinealectomy is possible in guinea-pigs and rats.

2. Pinealectomized male guinea-pigs show a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of the testes and seminal vesicles, over control pigs of the same litter.

3. Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, show a more advanced physiological state than their controls.

4. The pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight.

5. For several reasons, young rats are likely to prove better subjects for experimental pinealectomy than young guinea-pigs, and some evidence of hastened maturity has been obtained in this species.

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STUDIES ON THE PINEAL GLAND

II. CLINICAL OBSERVATIONS *

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INTRODUCTORY

The clinical aspects of pineal tumors have been abundantly discussed since 1909, when Frankl-Hochwart[10] suggested the possibility of a pathognomonic syndrome. Marburg[40] especially has developed the subject, emphasizing the association of adiposity, which he regards as an indication of overfunctioning of the gland. To this we shall return in the discussion of one of the cases here reported.

The salient factors of pineal symptomatology may be gleaned from the reports of about seventy cases of tumor of the gland. Of this number only twenty-two occurred before the age of puberty and these, therefore, represent the source of evidence of that special train of symptoms which we have come to associate with pineal disorders, namely, premature development in the realm of both primary and secondary sexual characters. In several of these cases, moreover, principally in the earlier reported ones, the case records are insufficient or wanting, and in five others no reference is made to the sex organs, although certain metabolic symptoms are noted. Of these, adiposity, drowsiness and polyuria are the most frequent, suggesting at once an implication of the pituitary, but the imperfect records preclude any possibility of settling this question at present. Regarding the other cases, of which there are about ten, we find that all but one are in young boys between the ages of 2 and 12 years. The exception is Marburg's case, a girl 9 years old.

Following Marburg's classification in his later paper (1913),[41] the symptoms recorded may be put down under three headings. 1. *General.*—These include all the usual signs of intracranial pressure, usually due to a secondary hydrocephalus, and need not be given in detail. 2. *Neighborhood.*—Of these the more important are dependent on pressure on the corpora quadrigemina, giving various oculomotor paralyses and pupillary disturbances, and also those by which the cerebellum is secondarily involved, with ataxia as the main symptom. 3. *Constitutional.*—It is here that we find the various changes for which the name "macrogenitosomia praecox" has been suggested. Coupled

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* From the Surgical Service of the Peter Bent Brigham Hospital.

with a general bodily overgrowth, the size of the primary sex organs is the most striking feature in the records of these cases. The penis and the testes are frequently described in these children as of adult proportions, and both pubic and axillary hair is noted to be similar in extent and abundance to that of maturity. Again, the change in voice to that of deep masculine type is recorded in one case as early as 5½ years. Mental precocity is also a well-marked symptom.

To sum up, then, the above syndrome usually occurs in boys before the age of puberty, and at necropsy in all cases a tumor replacing the pineal gland has been found. In the case of the girl, no disturbance of the sexual organs was apparent, adiposity being the only metabolic finding. If we are right in assuming that the pineal is a gland, and that its secretion exerts any influence on bodily processes, such evidence as we have would seem to indicate that this influence is exerted on inhibiting physical and mental adolescence.

REPORT OF CASES

During the past two years the following three cases have been observed in the surgical service at the Peter Bent Brigham Hospital. In one of them a tumor of the pineal was shown to be present at necropsy. The other two patients are still living, but with symptoms and signs sufficiently suggestive of pineal disturbance to justify their inclusion here.

It is quite possible that these conditions may be more frequent than is commonly supposed. Two cases have already been recorded by Dr. Cushing[11] in which the surmise of a pineal tumor was made. These gave the usual clinical picture. The two suspects among our present three cases are as follows. The first of these is a young girl:

CASE 1.—Surg. No. 1341. *Precocious adolescence: overgrowth: cranial enlargement. Callosal puncture.*

June 1, 1914, admission of Virginia G., aged 11; referred by Dr. H. T. Pershing of Denver, Colo.

Family History.—The patient's father and mother are living and in good health. There are two other normal children in the family, a boy and a girl, both younger than our patient.

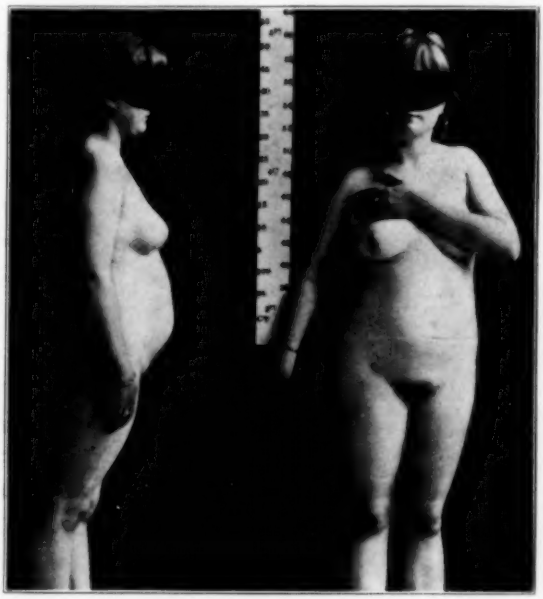
Personal History.—A full term baby, born without instruments and without particular difficulty; bottle fed; walked and talked at 18 months. At the age of 1 year it was noticed that her head was unusually large, and a diagnosis of hydrocephalus made by the family physician. Her body then began to develop abnormally, so that she has always been large for her age. Her mother describes her appetite as enormous.

Two years prior to admission she had what was apparently a period of polyuria. Subsequently she had a bad attack of typhoid fever, with relapse, lasting six months. Eyesight has been poor since babyhood and she has worn glasses for some time. Apparently there was an external strabismus of the left eye which was corrected by operation two years previously.

There has been a persistent but not increasing weakness of the right hand and arm since birth, so that the child early learned to use the left hand almost

exclusively, even in writing. For many years, also, she has been troubled with headaches, which have been frontal and bitemporal in situation. There has been no concomitant nausea, or vomiting, but some slight dizziness. These headaches have been less troublesome during the past two years.

Along with the overgrowth of the body there has been a precocious development of the secondary characters of sex. In August, 1913, when hardly 11 years old, the child first menstruated and she has since continued to do so regularly. Her bust became rounded and her bodily configuration was that of a girl beyond the ordinary age of puberty. The growth of pubic hair also started. Mentally, however, she was still a child, although not backward in school work. She finds mental application rather difficult. Her weight a year prior to admission was 98 pounds.



Figs. 1 and 2.—Case 1. Patient, aged 11; height, 152 cm.; weight, 52.3 kg.

Physical Examination.—A very well nourished and decidedly overgrown girl (Figs. 1 and 2). Height, 152 cm. (average normal for female of 11.5 years, 138.9 cm. (Boas). Weight, 52.3 kg. (average normal, 33.8 kg.); skin soft, moist, and pigmented; general increase in the subcutaneous adipose layer, the body looking plump and abdomen full; head very large, especially full in the frontal region, and definitely asymmetrical, the whole temporal bone of the left side being much more prominent than its fellow; neck full in the region of the thyroid and the isthmus of the gland palpable.

The breasts were very large and firm, areolae pink, the whole corresponding to the growth obtained at 15 or 16 years of age; pubic hair fairly abundant, and axillary hair present to a slight degree, but hair over the body in general lacking; hair on the scalp fine, silky, and abundant. The general contour of the body was that of a girl well past the age of puberty. Examination of

the fundi showed unusually large disks. On the left there was evidence of an old choroiditis with marked pigment upheaval and irregular shaped disk. Both disks were markedly pale, suggesting a primary atrophy.

In other respects the general physical and neurological examinations were negative.

The Roentgen-ray examination showed a hydrocephalic skull with signs of pressure. The sutures were plainly visible. The sella turcica showed very definite enlargement, the anteroposterior diameter being about 20 mm. The floor of the sella was more vertical than normal. The dorsum sellae was short but distinct. The clinoid processes could be made out. The metacarpal bones and phalanges were long and slender. There was a shadow in the region of the pineal body, presumably calcium deposit.

Urine negative; blood pressure and hemoglobin normal; differential blood count showed 6 per cent. eosinophils.

June 10 a callosal puncture was performed without altering her condition. She was discharged June 19, 1914.

Comment.—In this case, we have no positive means of knowing whether or not the pineal is the organ mainly at fault. The history and findings, however, are suggestive, and conform to the symptom complex of Frankl-Hochwart, except that the patient was a girl. Adiposity, though not great, was present to a definite degree, this, with the other points, making the case very similar to Marburg's.

An increase in the eosinophilic leukocytes should be mentioned, as attention will be called to this point in connection with Case 3.

The following case was also regarded as possibly one of macrogenitosomia praecox.

CASE 2.—Surg. No. 119. *Unusual precocity of adolescence and overgrowth. Epilepsy. Exploratory operation.*

May 17, 1913. Admission of Max W., aged 7½; referred by Dr. T. H. George of Cleveland, Ohio, with the complaint of precocious adolescence and epilepsy.

Family Hisstory.—Father and mother were living and well. The father was of small stature. There were two other normal boys in the family.

Personal History.—Birth normal and noninstrumental; weight at birth said to be 13 pounds. It was remarked a few days later that his genitalia were noticeably large. When 9 months old he had a bad fall down a flight of steps, but apparently suffered no immediate ill effects. There was no serious illness other than the present trouble.

Growth was rapid, and the patient had always been the tallest of his class in school. Three teeth appeared at 3 months of age and the second set was complete at the age of 7. When 3½ years old the voice had assumed adult characteristics.

Pubic and axillary hair were first noticed at two years of age and increased steadily in amount. Evidences of sexual instinct occurred at the age of three and a half. Masturbation was a continued feature. The disposition had always been irritable and stubborn.

Present Illness.—First evidence of epileptiform seizures occurred at the age of 3 years. These attacks consisted in an initial, momentary grimace, with groaning, turning of head to right and temporary loss of consciousness. Occasionally headache accompanied the seizures. The duration of attacks was thirty seconds to three minutes. They increased in frequency from the time of their onset until the present.

Physical Examination.—Although only 7½ years old, the patient looked like a boy of 15 or 16 (Fig. 3); weight, 35.2 kg. (average normal for age, 23 kg.); height, 145 cm. (average normal for age, 119 cm.); circumference of head, 53 cm.; axillary hair present; abundant "down" on upper lip; pubic hair thick and of mature, masculine type, but did not extend up on abdomen; external genitalia markedly overdeveloped, in no way differing from those of an adult male; flaccid penis, 9 cm. in length; thyroid cartilage prominent and thyroid gland distinctly palpable; teeth in good condition; second set fully established.

The fundi were slightly hyperemic; marked nystagmus to the right; voice deep and masculine; blood and urine examinations normal.

Subsequent Notes.—From three to six epileptiform attacks were noted daily; patient's disposition troublesome and mischievous. Discharged, untreated, May 30, 1913.

Fig. 3.—Case 2. Patient, aged 7½, with father; height, 145 cm.; weight, 35.2 kg.

June 17, 1914. Readmission; symptoms increased; headache more frequent; seizures occurred oftener; weight, 39.4 kg.; height, 145 cm.

Roentgen-ray examination of hands and feet showed development corresponding to that at the age of 18 years; inner aspect of skull somewhat irregular; venous channels plainly visible; sella was 6 mm. deep with antero-posterior diameter of 10 mm.; clinoid processes distinct.

June 27, 1914. Operation: puncture of right lateral ventricle; arachnoid very wet; membrane grayish and thickened; 20 c.c. fluid secured from puncture; fluid not under tension. A small section of tissue was removed from testis for histological examination.

July 13, 1914. Second operation: exploration of right hemisphere; dura appeared normal; brain under normal tension; arachnoid grayish and thickened, especially anteriorly where it was excessively vascular. By pricking the membrane a large amount of fluid was milked out. The process was evidently an old meningo-encephalitis with convolutional atrophy.

Subsequent Notes.—Convalescence uneventful. Convulsions continued, but not so frequent; no headache since operation. Examination of section of testis showed active, adult type with hyperplasia of interstitial cells. Discharged July 31, 1914.

Comment.—In this instance we are as yet unable to say what part the pineal may or may not be playing in the syndrome. Clinically, however, we are dealing with a symptom complex similar to that characterizing a pineal lesion, but without adiposity. The sexual side of the picture is decidedly in the foreground. There has been little intellectual attainment, the latter sphere having been greatly limited by the boy's environment.

In our third case the lesion was certified in full.

CASE 3.—Surg. No. 709. *Precocious adolescence. Intracranial symptoms with diagnosis of tuberculous meningitis. Xanthochromia. Necropsy. Pineal tumor.*

Dec. 22, 1913. Admission of S. K. B., aged 12; referred by Dr. J. B. Pratt of Boston, with the complaint of nausea and vomiting, intermittent headaches, and blurring of vision of two months' duration.

Family History.—A younger brother of the patient had died two years before, aged 5, from an "acute infection starting with a nasal discharge." The patient's father is a physician and he described this illness as "a meningeal complication after pneumonia."

Personal History.—The patient had always enjoyed good health; never had any serious illness, but had been subject to rather severe asthmatic attacks with spasms of coughing and expectoration, but never any hemoptysis.

The most striking feature of the boy's past was his rapid development, both physical and mental. He had always been athletic and very fond of outdoor sports, and excelled in competitions with other boys at school. In June, 1912, he weighed 72 pounds, and in June, 1913, this had increased to 112 pounds (a gain of 40 pounds in one year). A year previously, or when he was 11 years old, his mother noticed that his voice was changing. His mental development had been very noticeable, as exemplified by a more mature mental attitude shown by thoughtfulness and in other ways.

Present Illness.—In September, 1913, he had left home for his boarding school in perfect physical condition. October 14 he had an acute exacerbation of his bronchial asthma and four days later was taken home. At this time he had a profuse, foul smelling, greenish nasal discharge. This attack, which was accompanied by more or less frontal headache, lasted three weeks, and there was deafness in both ears which persisted for a few weeks.

October 21 the father was struck by the boy's widely-dilated pupils and a strange, staring expression of his face. Since then the pupils had been unequal, sometimes the right being larger and at other times the left.

Headache was present from the middle of October. At the outset of the trouble there had been occasional attacks of nausea and vomiting and these increased in frequency up to the time of admission.

At times during November and December he complained of transient blurring of vision. Two weeks before admission his fundi and visual fields were examined by a competent ophthalmologist and found to be normal.

During the first ten days of December there was a definite polyuria—four quarts in twenty-four hours on one occasion. Examination showed merely a low specific gravity: sugar was never found. A cranial roentgenogram was negative. The blood showed 16 per cent. of eosinophils.

For six weeks before admission his temperature was subnormal. Vertigo was present during the previous week. Two days before coming to the hospital there was the first indication of diplopia.

Physical Exaination.—A lean, fine looking boy of 12 years, evidently large for his age; height, 5 ft. 3 in.; weight, 97 pounds—17 pounds less than at the outset of the trouble; skin showed a brownish pigmentation or discoloration, possibly due to exposure to the sun; long bones noticeably large, especially at their lower ends; external genitalia overdeveloped for the age of the patient; pubic and axillary hair present; abundant "down" on face.

Neck slightly but definitely stiff; some occipital tenderness; Kernig's sign markedly positive on both sides; slight conjunctivitis.

Neurological: Left pupil larger than right; both react to light and accommodation; diplopia present on looking to right, but not to left; movements of globes not well coördinated; fundi showed swelling of 2½ D. on right and 1½ D. on left; marked venous engorgement and tortuosity with slight embedding of vessels at disk margins.

Tests for the other cranial nerves showed an impaired olfactory sense and a slight deviation of the tongue to the left.

The Romberg was suggestive, with a good deal of swaying from side to side, but the patient was weak and had been confined to bed for several weeks. There was a tendency to stagger to the right when walking, and definite ataxia of left arm, as shown by finger tests.

Roentgen-ray examination of the head was negative, with normal sella; urine and stool examinations negative. Repeated examinations of the sputum showed no acid-fast organisms; tuberculin and Wassermann reactions negative; blood pressure and hemoglobin normal; differential white count showed 9 per cent. eosinophils.

Subsequent Notes.—December 26, lumbar puncture and withdrawal of 40 c.c. of a straw colored, cloudy fluid. The cell count showed 1,011 old, disintegrating, red cells (no fresh blood contamination) and eighty-five white cells per c.mm.; Fehling's test positive; Noguchi test positive; no acid-fast organisms found.

December 27. Examination of the fundi showed elevation of 3 D. right and 2½ D. left; faint linear hemorrhages noted, and venous engorgement more marked.

December 28. Von Pirquet reaction negative; attack of numbness of right hand, arm, and right side of body, accompanied by motor aphasia.

December 30. Temperature subnormal since December 23; Wassermann reaction of spinal fluid negative.

January 1. The patient remained in the hospital only ten days and during this time his condition did not change essentially. He was discharged on this date. The diagnosis was uncertain. The possibility of tuberculous meningitis and brain tumor was discussed. Decompression was advised and refused.

After his stay in the hospital the patient was removed to his home in the country where he became progressively worse and had occasional periods of deep somnolence. He complained of no pain. The Kernig remained positive.

Subsequent History.—January 28 he complained of numbness of the right hand and had a right sided convulsion. He remained practically comatose and was readmitted to the hospital, where an examination of the fundi showed an elevation of 5 to 6 D. on both sides. The rigidity of the neck was increased; reflexes not elicited at knee, ankle or elbow; plantar response questionable; persistent weakness of right and possibly both abducentes; a Kernig sign at 90 degrees persisted.

In order to determine the presence or abscence of hydrocephalus, a diagnostic ventricular puncture was performed under local anesthesia. The needle was inserted to a depth of only 2½ cm. at Kocher's point and entered a dilated ventricular cavity. Fifty or 60 c.c. of yellowish fluid, such as was previously removed from the lumbar region, was withdrawn, examination of which showed: 561 old red cells per c.mm. (no fresh blood); 17 lymphocytes; Fehling's test positive.

The patient seemed to improve temporarily after the tapping, took nourishment and responded to stimuli, but suddenly, three hours later, the respirations became shallow and he rapidly failed.

Comment.—At the outset, the symptoms of headache, nausea and vomiting, vertigo and blurred vision, and the physical signs of choked disk and diplopia made one think at once of an intracranial new growth. This idea was furthered later by the right-sided convulsion,. which was followed by numbness of the right arm and leg, accompanied by aphasia. The rapidly increasing elevation of the optic disks also made it especially hard to rule out brain tumor. However, on careful examination of all the evidence, other factors appeared to play an even greater part in the syndrome and to cause the balance to swing over to the diagnosis of a probable infectious process, possibly similar to that from which his brother had died.

There was the history of a chronic nasal catarrh with an acute exacerbation a few weeks before the onset of the illness, followed by a transient deafness in both ears lasting two weeks. Then the cervical rigidity, positive Kernig's sign, and a beginning conjunctivitis was suggestive. Adding to this the peculiar character of the spinal fluid, its high count of mononuclear cells without any polymorphonuclear elements, and positive globulin and Fehling's tests, it seemed likely that we had to deal with a tuberculous meningitis. The symptoms of general pressure were by no means against such a diagnosis, nor were the variable pupillary and other phenomena associated with the cranial nerves. Two points, however, could not be overlooked in making a tuberculous lesion responsible for the condition, namely, the negative von Pirquet test and the negative examination of the lungs. The report on guinea-pigs inoculated with the patient's spinal fluid was not available at the time of his first discharge. Furthermore, no tubercle bacilli were found in smears of the spinal fluid or in the sputum.

In view of the necropsy findings, we must now consider a number of points which were not sufficiently noted in the presence of other symptoms which seemed to hold the forefront of the picture. The boy was very perceptibly overgrown, a fact noted by Dr. Pratt when referring him to the hospital. At the age of 12 years he measured 5 ft. 3 in. in height and two months before his illness weighed 114 pounds. A year previously his mother had noticed the change in voice to that of the adult masculine type. His father, too, had recently noted

a more mature mental attitude of thought and action. On examination the well developed, athletic figure was apparent. The brownish pigmentation of the skin was put down, at first, as due to exposure to the sun, but on more careful scrutiny the distribution of this coloring was not that usually seen in persons so exposed. The external genitalia were fully developed and there was abundant pubic and axillary hair, as well as an adolescent beard on the chin. These facts are of course very significant when one is acquainted with the intracranial postmortem examination, but before death it was very easy to attribute the physical overdevelopment to the boy's athletic nature and participation in outdoor sports.

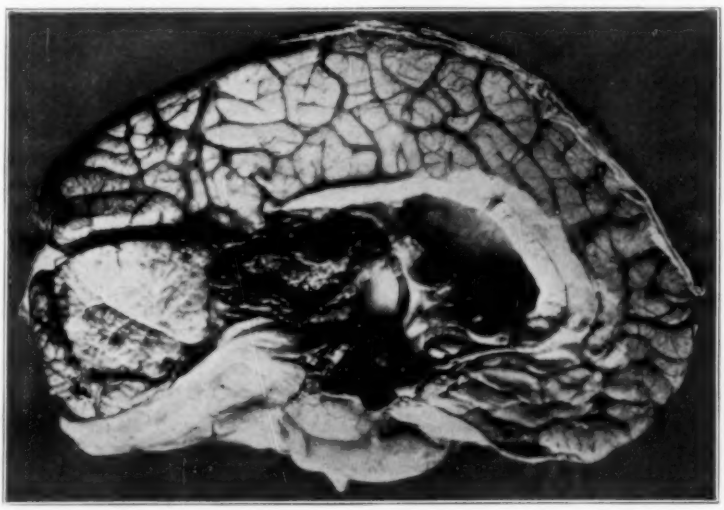


Fig. 4.—Case 3. Median section of brain showing tumor of the pineal region with implantation in floor of third ventricle; also secondary ventricular dilatation.

In the words of Frankl-Hochwart, "When one finds in a very young individual (boy), along with the general symptoms of tumor, as well as the local signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor." We had before us a similar picture, obscured though it was by other factors.

One feature of the pineal syndrome was lacking, namely, the adiposity which has been dwelt on by most writers on this subject. In regard to this condition, which may be consequent on or associated with

disturbed functions of the pineal gland, there are, at present, three views: first, that of Marburg, that obesity is one of the expressions of overfunctioning of the gland, hyperpinealism; second, the view held by other authors, namely, that it may be due to a pineal tumor supposedly causing a lessened functioning of the gland, hypopinealism; and third, the view that the adiposity is due to secondary changes in the hypophysis brought about by the pressure excited by internal hydrocephalus (Cushing[11]).

So far, Marburg's case of so-called hyperpinealism, with its accompanying adiposity, is the only one attributed to glandular overactivity, and, as Kidd says,

> Even absence of any recognizable histological changes in the pituitary or other glands in such cases does not exclude the possibility of associated dispituitarism due to subtle metabolic or chemical changes of which, at present, we have no knowledge. Then again, adiposity occurs in so many other conditions and its modes of production are still so obscure, that we must conclude, I think, that it is uncertain whether hyperpinealism in man ever causes adiposity per se.

Of the sixty cases of pineal tumor collected by Bailey and Jelliffe[2] in 1911, fourteen are recorded as being associated with adiposity to a greater or less degree. Marburg's case is included in this series. The hypophysis was examined in very few of these cases, so it cannot, as the authors state, be shown by statistics what relation this organ may have borne to the syndrome. There is in all cases, however, a marked degree of internal hydrocephalus, and this factor may well disturb the functioning of the pituitary even though the cells of the latter remain histologically normal.

Xanthochromia.—Mention has been made of the peculiar color and characteristics of the spinal fluid in the case under consideration, obtained both by lumbar puncture and by tapping of the lateral ventricle. Such a condition of the cerebrospinal fluid has been termed xanthochromia and is usually associated with an increase in the cellular and albuminous elements of the fluid, particularly fibrinogen, these substances causing the production of the so-called "massive coagulation." Several cases showing this condition were collected by Froin[21] in 1903, and since then a number of others have been reported.

A lesion which causes a constriction or compression of the meninges around the cord, thus making the subarachnoid space in the lumbar region a closed cavity is likely to produce such a condition of the fluid. Such lesions have been associated with meningomyelitis, tuberculous meningitis, Landry's paralysis, tumors of the cord, and, rarely, cerebrospinal lues.

Into a closed cavity of this sort the elements necessary to the production of "massive coagulation and xanthochromia" could come in

two ways; (1) by transudation or (2) by capillary hemorrhage. The exudative lesions like myelitis and meningitis easily account for the products accumulated through transudation, and this process is no doubt the most usual one. The origin of the capillary hemorrhages is not so clear, but in the few cases reported they have been associated with tumor of the cord.

In view of these facts, Mestrezat[48] concludes that the physical and chemical properties of the cerebrospinal fluid, together with the clinical and necropsy findings, demonstrate the reality of a closed cavity and the existence of stasis of the fluid as necessary to the production of the syndrome.

In cases of xanthochromia previously reported, the fluid has always been obtained by lumbar puncture. In our patient, the fluid taken from the ventricle was identical with that previously procured from the lumbar region. Its color and cellular content corresponded with the other cases reported. Massive coagulation, however, did not exist, although albumin was present to a definite degree, as shown by the Noguchi test.

Many tumors which grow into the ventricles are accompanied by xanthochromia due, doubtless, to the escape of blood cells from the surface of the tumor into the fluid. We have seen a number of examples in this clinic.

PATHOLOGY

A study of the diseases to which the pineal body is subject has been confined almost exclusively to the different varieties of tumors which have been found to arise either from the gland itself or from those structures which lie in its immediate neighborhood and therefore involve the pineal secondarily. Very rarely conditions other than tumor have been mentioned in connection with pineal pathology, but these play an inconspicuous and perhaps dubious part in this chapter of the study of the gland.

Cysts seem to be the most common and earliest recognized of the tumors of the pineal, a "hydrops cysticus" of this organ having been described by Virchow[77] in 1863. Marburg in 1909[40] gave an excellent description of the types of pineal cysts. These he divides into two classes: (1) involution, formed by the degeneration of areas of pineal substance due to sclerosis of the blood vessels; and (2) retention, arising from the "recessus pinealis," and lined by ependyma, by which they are distinguished from the involution type.

Next in point of frequency come the teratoms, for a classical description of which all authors refer back to Weigert's article[79] of 1875. In brief, the main facts which have been assembled regarding this type of pineal tumor are as follows: They occur almost exclusively

in children, Neumann's patient of 27 being the only exception.[51] All others were under 15 years of age. The tumor occurs always in the anterior portion of the pineal, and this fact has led some authors, notably Askanazy,[1] to ascribe their origin to the anlage of the parietal eye of the lower vertebrates. Marburg confirms this theory by his discovery of the remains of the "nervus parietalis and ganglion parietale" in the most anterior part of the pineal in the neighborhood of the taenia habenulae. The elements contained in these tumors are the usual ones found in the teratomas of other organs, namely, hair, cartilage, sebaceous glands, smooth muscle fibers, fatty tissue and occa-

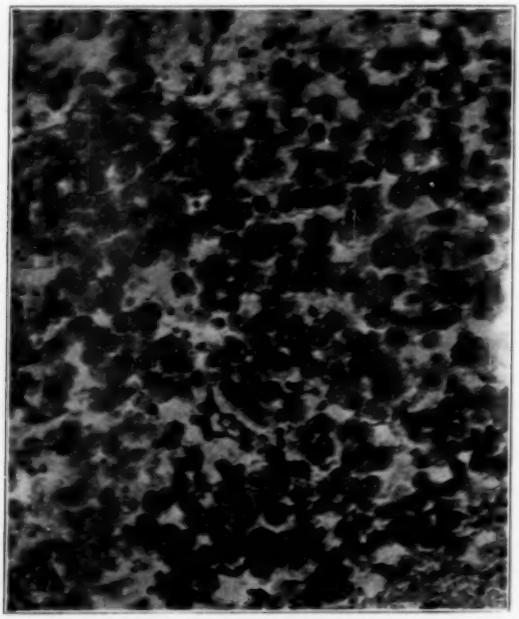


Fig. 5.—Showing character of cell masses (Mag. × 250).

sionally axis cylinders. The cases of teratoma on record are those described by Weigert, Coats,[10] Falkson,[16] Ogle[37] (two cases), Gauderer,[23] Gutzeit,[26] P. Neumann, Hueter,[34] Frankl-Hochwart,[19] and Bailey and Jelliffe.[2]

A great deal of discussion arises as to whether or not the other recorded types of tumor are distinct enough to be classified separately. Marburg groups all tumors of the pineal other than cysts and teratomas into a general class of "mixed tumors," and there is undoubtedly much to be said in behalf of this method. From a general survey of the cases

described, however, it seems probable that four other fairly distinct varieties may be recognized, namely, (1) gliomas (in the cases of Duffin,[13] Schultz,[68] Lawrence,[38] Nothnagel's second case,[54] and Raymond and Claude[61]); (2) sarcomas (Gowers,[25] Kny,[36] M. Neumann's second case, Nothnagel's first case, Pontoppidan,[60] Feilschenfeld,[17] and Hösslin[32]); (3) carcinomas (Massot,[42] Daly,[12] Förster,[18] and Hempel[29]); (4) psammoma (Friedreich,[20] Blanquinque[6] and possibly Wernicke[80]). From a histological standpoint there is no reason why pure tumors of these four distinct types should not arise from the pineal. The four types of mother cells which produce them

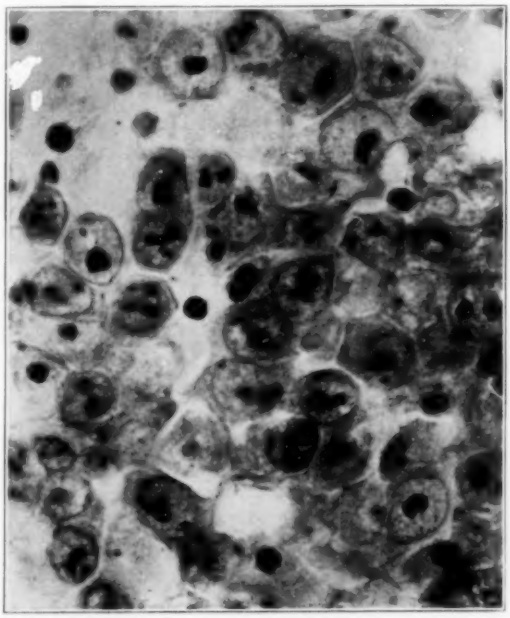


Fig. 6.—Showing character of cells with irregular chromatin and nuclear figures (Mag. × 1,000).

are a constant anatomical element of the gland, and there is no basis for questioning the pathological diagnoses made, at least by the later authors.

That there is, however, a large class of pineal tumors which cannot be put down as conforming on the whole to any one specific type, is likewise true. For the present, therefore, it would seem best to follow Marburg and assemble these under the heading of "mixed tumors." In this group possibly belong the angiosarcoma of Hart;[27] the gliosarcomas of Howell's three cases,[33] and that of Zenner;[82] the neuro-

glioma of M. Neumann's first case;[50] the psammosarcomas of König,[37] and Oestreich and Slawyk;[56] the chorio-epitheliomas of Askanazy[3] and of Goldzeiher;[24] the unclassified tumors of Blane,[5] Schmidt,[67] Schearer,[65] and Schmid;[66] and the "mixed tumors" or Marburg and of Pappenheimer.[58] Possibly we should put the adenoma described by Meyer,[44] and the epithelioma described by Estèves and Beatti[15] in this larger class also.

Turning now to the extremely rare instances of disease of the pineal, other than tumors, we find hemorrhage described twice (Simon,[70] Zeigler[83]); abscess once (Birsch-Hirschfeld, quoted by Marburg); and syphilis once (Lord[39]); while Pontoppidan was unable to make an exact diagnosis in his case between syphilis and sarcoma.

Pathological Report.—The postmortem studies in our own case are as follows. An examination of the head only was permitted after death. This limited necropsy was performed by Professor Councilman five hours later. His description of the findings is as follows:

The brain has been removed and bisected longitudinally (Fig. 4). The ventricles are dilated. In the posterior half of the lateral ventricle, in the region between the tail of the corpus callosum, which is elevated, and the medulla, in the region of the pineal gland, there is a tumor mass 5 cm. long, extending from the anterior edge of the cerebellum to within 4 mm. of the fornix, for a distance of 4.6 cm. Between the medulla and the corpus callosum the tumor measures 2.5 cm. In the center of the tumor mass is a large blood clot. The tumor seems to be composed of a soft, very much congested material, probably in part hemorrhage. It is adherent to the structures below it. In the floor of the greatly dilated third ventricle, which measures 2.5 cm. antero-posteriorly, there is a similar mass of tumor tissue, 2 by 2 cm., in no way connected with the primary tumor tissue. This is evidently an intraventricular implantation of the primary tumor.

Microscopical Examination.—Various parts of the tumor and its ventricular implantation show essentially the same structure. It is composed (Figs. 5 and 6) of loosely placed cells of an epithelial character without any very definite arrangement. They have large nuclei and a small amount of pale cytoplasm. There is no definite stroma. Between the cell masses, in places there is abundant hemorrhage, and in others great numbers of cells of the lymphoid type. The appearance resembles the cellular tumors of the hypophysis; in the nuclei are large amounts of chromatin and granules. At one place, taken from the lower aspect of the tumor, there is a small amount of adherent choroid plexus which shows very slight reactive new growth. The implanted fragment of the tumor shows some invasion of the pituitary body by the growth (Fig. 7). Degenerative processes in the tumor are common, there being comparatively large areas composed of necrotic cells. Various cell types other than the usual are encountered; around them are giant cells with peripheral nuclei with division figures, of normal type, in the single nuclei. Nuclear figures in small numbers are found in nearly every cell. Most of the epithelial cells of the tumor take the hematoxylin stains very intensively; they all seem to be of about the same type. There are no concretions in the tissue.

Diagnosis: Struma of the pineal gland.

Comment.—The tumor mass on the surface of the third ventricle is not to be regarded as a metastasis, but as a surface implantation

due to single cells or portions of the tumor which, having become detached, have formed a junction with the surface of the ventricle, the extension here being of the same character as the tumor implantations which only occur on the peritoneal surface.

That the tumor was one of very rapid growth is shown by the many nuclear figures and evidences of indirect division, and yet there was no tendency to invasion except in the case of the hypophysis (Fig. 7). The character of the cells here corresponded to that noted elsewhere, but the supporting stroma was more evident, owing to the

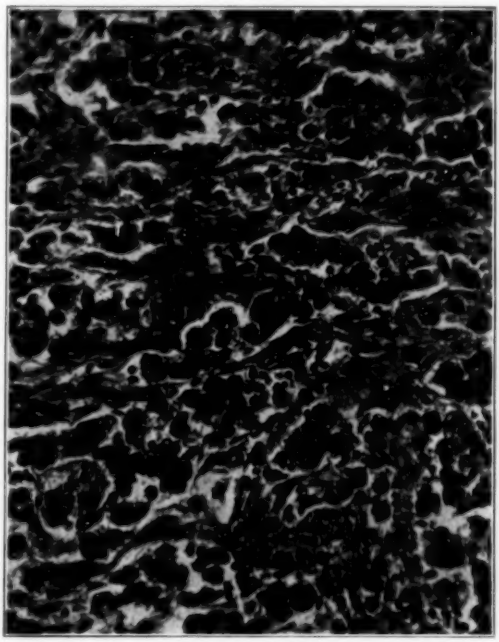


Fig. 7.—Showing invasion of anterior lobe of the pituitary body by tumor (Mag. × 250).

difference in structure of the tissue invaded, and the resulting appearance was more like that of a carcinoma.

A striking feature of the tumor as a whole was the great number of lymphoid cells it contained. These were present both in large masses grouped together, and also as scattered elements throughout the growth without definite arrangement. This enormous development of lymphoid tissue in a patient 12 years of age brings out the possibility of associated lesions elsewhere in the body, especially in connection

with the thymus and lymph glands. The limited necropsy prevented studies of these tissues.

The question whether such a tumor represents an overfunctioning or an underfunctioning of the gland cannot be decided definitely on the basis of the anatomical findings. The structure corresponded in many respects to the diffuse struma often seen in the pituitary and which usually accompanies states of pituitary insufficiency. It is difficult to tell from the histological appearance alone of a ductless gland whether or not this is functionally overactive or underactive, though in the case of the thyroid we assume that we can do so, and possibly we may also in the pituitary gland. If this particular struma of the pineal which we are considering represents functionally overactive cells, the symptoms would be explained as Marburg has explained them on the basis of hyperpinealism, and the experimental feeding observations by Dana and McCord might be interpreted as lending support to such a view. Two points, however, render such a view improbable. In the first place, the cells show an extreme rapidity of growth, indicating an active formative faculty which is usually associated with a loss of specific function. Further, the cytoplasm of the cells contains no demonstrable granules, and these are usually regarded as representing functional activity.

It is our impression, from what we know of the physiology of the normal gland, as well as from the results of Foà's and our own experimental observations, that sexual ripening occurs when the pineal ceases to be functionally active, or when it is removed, and on this basis we incline to the belief that the tumor in most of these clinical cases is associated with an inhibition of the normal products of pineal secretion. If this were really the case, however, one would suppose that glandular feeding would postpone adolescence, but from the observations of Dana and McCord the reverse seems to occur. Our own studies in this direction with the feeding of young guinea-pigs and rats were not conclusive and it is a matter which deserves further study.

SUMMARY

1. Extirpation of the pineal in young chickens and lower animals tends to hasten normal maturity.

2. Tumors of the pineal gland in children occurring before the age of puberty usually give rise to a syndrome characterized by precocious adolescence.

3. Feeding the gland substance to young animals is said to have the same effect as extirpation, but the observations are somewhat inconclusive.

4. A report of three cases of supposed pineal tumor, one of which was certified by necropsy, is offered as a further contribution to the study of this gland.

I take this opportunity of expressing to Dr. Harvey Cushing my deep gratitude for the help, both by suggestion and inspiration, with which he has guided this work, and for his kind permission to publish the cases from his clinic. I also wish to thank Dr. W. T. Councilman for his advice and cooperation concerning the pathological features of the paper.

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THE ADJUSTMENT OF PRESSURES IN INDUCED PNEUMOTHORAX

WITH ESPECIAL REGARD TO THE MOBILITY OF THE MEDIASTINUM AS INDICATED BY THE MANOMETER *

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During the treatment of phthisis by compression of the lung, there is need of exercising a nice judgment regarding the degree of pressure that should be maintained throughout a long series of injections. Our experience is that the displacement of the mediastinum is of first importance in the adjustment of pressure at any time, and our purpose is to show how this may be estimated with fair accuracy by the aid of the manometer and without the help of the Roentgen ray when the result of physical examination is uncertain.

The first consideration is to obtain a satisfactory collapse of the diseased lung; but while one is trying to effect this a compromise in the pressure desired may have to be made for the safety of the less diseased lung and of the heart. Cases in which collapse of the lung takes place easily seem rarely to suffer strain to either organ if the collapse is gradually induced, and these are the cases in which the mediastinum will usually be found movable.

The cases in which collapse of the lung is more difficult, unless this difficulty is due solely to an induration of the lung, will, because of thickening of the pleura and adhesions, have a much less easily displaced mediastinum. This relative rigidity of the mediastinum then becomes a great protection to the very cases that require considerable pressure to reduce the size of the lung. With lateral adhesions in the upper part of the thorax, a marked displacement of the mediastinum may nevertheless take place.

The effect that the extra work will have on the functionating lung is a source of continual anxiety. The beneficial influences, which according to accepted theories account for its improvement, may be sufficient to arrest progress of disease or render it quiescent; but during the long course of treatment indolent progress may be noted after earlier marked improvement. This lung becomes enlarged, emphysematous and elongated. Lord[1] considers the arguments in favor of the

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1. Lord: Diseases of Bronchi, Lungs and Pleura, 1915, p. 584.

beneficial influence of the overwork of the better lung as invalid. Aron[2] sees little chance for healing of disease in the better lung because of its greater respiratory movement and finds it impossible to imagine that the better lung can heal under such conditions. There is such danger to a diseased lung from the greater excursion that he urges that on no account should compression be pushed so far that breathing is stopped entirely in the compressed lung. The type of respiration becomes modified as is best suited to the need of the individual at any one time (Brown[3]) and Aron[2] finds in man that the untreated lung breathes with increasing depth the more the treated lung is excluded from respiration, as is shown by greater fluctuations of a manometer connected with the pleural cavity of the functionating lung. Aron's[4] experiments on animals show the concurrent changes of pressure in the pleura of the functionating side while one lung is gradually excluded from respiration. After a mean pressure of zero has been reached the depth of respiration which, following an initial increase, has steadily lessened and has been compensated by increased frequency of respiration, promptly increases with lessened frequency of breathing, and at the same time there is a very marked rise in blood pressure. The lessening depth of respiration of the functionating lung is shown in the pleural cavity by the negative pressure's becoming less marked on inspiration and more marked on expiration, thus showing a decreased amplitude.

There may be embarrassment to the circulation with either fixed or movable mediastinum, since, on the one hand, rigidity may cause pressure to be brought to bear on the heart, vessels and nerves, and, on the other hand, flexibility will permit varying tension, kinking, strain and pressure as well.

The right heart, besides the handicap of diminished vascular area in the collapsed or compressed lung and the loss in part of the pump action of the thorax, has to undertake the maintenance of an increased circulation in the functionating lung, and is further embarrassed by more or less lateral displacement (sometimes with a twist on either vertical or horizontal axis or both), and the pressure of the relatively unyielding gas cavity. Moreover, the heart is the first to feel the effect of diminished oxygenation, and the general need of oxygen also causes a rise in pressure in the systemic circulation. Pressure or strain on nerves may also affect the innervation. The fact that the right heart hypertrophies in man as well as in animal experiments, has been shown at necropsy; but it has also been shown that it sometimes fails to do so. Improvement in the heart's action through lessened toxemia and

2. Aron: Berl. klin. Wchnschr., 1913, L, 305.
3. Brown, T. R.: Modern Medicine, Osler and McCrae, 1907, iii, 549.
4. Aron: Virchows Arch. f. path. Anat., 1896, cxlv.

improved general condition more than make up for these embarrassments in favorable cases. The heart also may benefit by being enabled to return to a more normal position after previous great displacement due to a contracted lung.

As to a satisfactory collapse of the diseased lung, various writers set different ideals of attainment, though all aim at the exclusion, if possible, of the treated lung from respiration. Saugman and Hansen,[5] while approving Foralnini's objective of compression as a curative measure, were able to obtain complete compression in only 15 per cent. of their cases. On the other hand, Dunham and Rockhill,[6] using the operation as a palliative measure and controlling their work with the Roentgen ray, found that refilling should be frequent and the gas pressure slight, the amount of gas injected being just sufficient to keep the lung collapsed and no more, a zero inspiratory pressure being more than enough. Brauer and Spengler[7] emphasize the general rule that the better and larger the pneumothorax obtained the less need be the pressure, and they consider the object of the operation has been reached as soon as there is no negative inspiratory pressure. When the lung is not too dense, a pressure of 2 to 4 cm. of water is considered by various writers to be sufficient to keep the lung compressed if there are no adhesions. This pressure, if well borne, may be increased to 7 to 8 cm. If adhesions remain, possibly 40 cm. may be necessary (Rist[8]). Saugman has maintained a pressure of 20 to 30 cm. of water for months, but has never exceeded 8 cm. of mercury (108.8 cm. H_2O), while Brauer's limit has been 4.5 cm. Hg. Davies[9] considers it useless to persevere in the separation of adhesions when a pressure greater than 1 cm. Hg (13.6 cm. H_2O) is necessary.

Exclusion of the lung from respiration becomes from the standpoint of practice, a relative matter, since the frequency of refills necessary to maintain a consistent pressure is scarcely practicable, and in the intervals considerable reexpansion may take place. When the pneumothorax is established, an optimum point of pressure is usually found for each individual, determined for him mainly by the degree of tension the mediastinum will bear.

It has been shown by experiment that those animals bear pneumothorax best in which the elasticity of the mediastinum best resists displacement (Bruns[10]). The mediastinum is strengthened also by the deposit of fat. Man is fortunate in having a mediastinum with fair

5. Saugman and Hansen: Beitr. z. Klin. d. Tuberk., 1910, xv, 303.
6. Dunham and Rockhill: Jour. Am. Med. Assn., 1913, lxi, 826.
7. Brauer and Spengler: Beitr. z. Klin. d. Tuberk., 1909, xiv, 419.
8. Rist: Quart. Jour. Med., 1913, vi, 22.
9. Davies: Brit. Med. Jour., April 25, 1914, No. 2782, p. 897.
10. Bruns: Beitr. z. Klin. d. Tuberk., 1909, xii, 1.

elastic tension because of the relatively small distance between the heart and the sternum. However, at the site of the atrophied thymus there is a weak area which extends from the second to the fourth cartilage and may be 3 or 4 cm. deep, filled with loose connective tissue and fat. Another area where the pleura of the right side is relatively unsupported lies between the aorta and esophagus between the fifth and twelfth vertebrae (Nitsch[11]). At these situations the pleurae are capable of further distention after a certain pressure, which first causes a general displacement of the mediastinum, has been passed. There are apparently great individual differences in the resistance of the pleurae to pressure. A healthy pleura will bear a considerable positive pressure from inflation without causing dyspnea. A recently inflamed pleura becomes relaxed and yields more readily to pressure than the normal pleura, while more chronic intrathoracic inflammation and thickening increase the resistance. Pressure is found to be borne with less dyspnea when the pleura is thickened than when it is thin. This may be seen in pleural effusion, which, when recent and with a lower pressure, produces greater dyspnea than when the pleura is thickened and the pressure is higher.

For determining the pressure that will be the best compromise for the individual case, it is, therefore, important to take into consideration the degree of movability or rigidity of the mediastinum. The index of this is the position of the heart which it may or may not be possible to locate accurately by physical examination. The Roentgen ray is not always available, or it may be impossible to use it at every seance; but without changing the position of the patient the manometer gives information as to mediastinal displacement which serves as a guide at every refill. Naturally, information will be incomplete during the earlier inflations, at least until the zero point has been approached.

Von Muralt,[12] and Hamman and Sloan,[13] also, state that the manometer may indicate a too movable or too rigid mediastinum. Their views, however, are completely at variance. Von Muralt says that other things being equal, a flexible mediastinum is shown by a rapid rise in pressure with a small respiratory movement of the fluid in the manometer; a rigid mediastinum by a slow rise in pressure with large respiratory movement of the fluid. Hamman and Sloan hold that a slow increase in pressure with wide respiratory variation, indicates a flexible mediastinum; a rapid increase in pressure with small respiratory variations, a rigid mediastinum.

11. Nitsch: Beitr. z. Klin. d. Tuberk., 1911, xviii, 359.
12. Von Muralt: Beitr. z. Klin. d. Tuberk., 1911, xviii, 359.
13. Hamman and Sloan: Bull. Johns Hopkins Hosp., 1913, xxiv, 53.

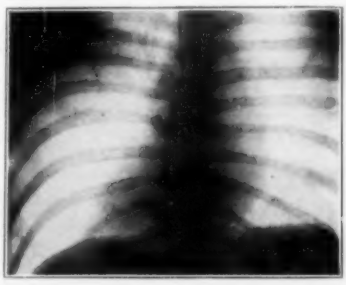
Contrary to these writers we[14] have found that a flexible mediastinum is shown by a slow rise in pressure with relatively small amplitude of movement of the fluid in the manometer on breathing, and a rigid mediastinum by a more rapid rise in pressure with relatively large amplitude. The slow rise in pressure when the mediastinum is unduly flexible is so obvious that it seems probable that von Muralt has not correctly stated his position. In his paper some ambiguity of the context suggests that this is so. Moreover, with a flexible mediastinum there are frequently to be noticed certain relatively stationary points at which there is no further rise of pressure after one, or even two, deciliters of gas have been introduced. These points are most frequently noticed when the mean pressure is near zero. The oscillations are also sluggish when the mediastinum is movable. When the mediastinum is more rigid the stationary points are not in evidence and the movement of the fluid in the manometer is more abrupt. These observations, recorded in an earlier paper, are in accord with the following theoretical considerations:

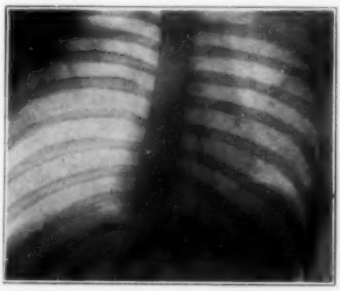
The position of the mediastinum at any time is accepted as one of equipoise between varying tensions of the two pleural cavities, the resultants of several factors, chiefly the elasticities of the lungs (West[15]). When the tension of one pleural cavity is lessened "the heart, the most delicate index of a change of tension on either side," will move towards the side on which the intrapleural tension is greater, i. e., on which the negative pressure is more marked, "'pushed in that direction by a force equal to the differences of those in the two pleural cavities" (Emerson[16]). In expiration, with a general relaxation of the thoracic wall and diaphragm, this position of equilibrium of the mediastinum necessarily exists, and during quiet respiration the same condition obtains, since the central tendon of the diaphragm does not stir. During more active inspiratory movement, however, modifying forces come into play so that the position of the mediastinum becomes a resultant of the antagonistic intrapleural tensions and the tension put on the mediastinum by the combined influence of the descent of the diaphragm and deepening of the thorax. The entrance of gas into one pleural cavity will, however, relax the diaphragm on that side and its dome will become lowered. This permits the mediastinum to yield itself the more readily to satisfy the variable tensions of the two pleural cavities. Irrespective of prevailing intrapleural tensions, inspiration will have the effect of flattening the curves, so to speak, of the irregular mass forming the mediastinum. This would even be

14. Parfitt and Crombie: Canad. Med. Assn. Jour., 1915, v, 373, 489.
15. West: Intrapleural Tension, System of Medicine, Allbutt and Rolleston, 1909, v.
16. Emerson: Johns Hopkins Hosp. Rep., 1903, xi.

the case in an open elastic cage with bulging central partition if the anteroposterior and vertical diameters were enlarged. This stretching with flattening of the bulge of the mediastinum on inspiration becomes of great importance in open pneumothorax as an aid to the respiration of the sound lung, as pointed out by Sehrwald.[17] Thereby a greater intrapleural tension is created on the sound side which is a necessary factor for its increased respiration.

The differences of tension between the pleural cavities while a closed pneumothorax is being induced is shown in the tables of Aron's[4] experiments. Though these were obtained in animals, analogous results would be expected in man. As might be anticipated, the actual differences in tension between the two cavities at each phase of respiration shows a constant increase in tension in favor of the





Figs. 1 and 2.—Fig. 1: Full inspiration (Case 1). Fig. 2: Full expiration (Case 1). Movable mediastinum; roentgenograms of chest taken the third day after the refill of April 3, 1915 (see Fig. 3).

pleural cavity of the functionating lung. Except for a very short time early in the operation, this difference of tension is much greater on inspiration. If relative intrapleural tension alone adjusts the position of the mediastinum, it would at first sight seem that the mediastinum should move toward the sound side on inspiration and away from it on expiration. That the reverse movement obtains is shown by the fluoroscope and roentgenogram (Figs. 1 and 2), and on inspiration the mediastinum is seen to move toward the pneumothorax cavity and away from it on expiration. The degree of this movement will necessarily depend on the relatve mobility of the mediastinum. If flexible, the movement is much more marked when there is considerable gas in the cavity than when it is relatively empty. In the latter instance a more normal condition is approached, since the diaphragm is less

17. Sehrwald: Deutsch. med. Wchnschr., Aug. 22, 1889; quoted by Emerson, Note 16.

relaxed, the intrapleural tension is increased and there is less necessity for a readjustment of the position of the mediastinum. The explanation of the movement of the mediastinum toward the pneumothorax cavity given by Bittorf,[18] and Saugman and Hansen,[5] also, is that the inspiratory increase of tension in the pneumothorax cavity causes the mediastinum to move toward that cavity. Because of the experiments just mentioned this explanation demands consideration, since there is a relatively greater tension on inspiration in the pleural cavity of the functionating lung. The enlarged thorax on expiration will, however, cause a shift of the mediastinum to the pneumothorax side through the altered intrathoracic pressure, modified, of course, by the restraining opposed tension of the sound pleural cavity. The values of the pressures recorded in the pleural cavity of the functionating side must be accepted with some reservation since on this side the force of cohesion is practically unimpaired and this force, according to Brauer[19] and Roth,[20] abolishes the negative pressure which becomes a fact only after a pneumothorax has arisen.

The mediastinum, then, in an artificial pneumothorax, plays an active part on inspiration, and a passive part on expiration, when its position is determined by the opposing intrapleural tensions.

Therefore, when the mediastinum is movable the inspiratory enlargement of the thoracic space on the side of the pneumothorax will be reduced by the encroachment of the mediastinum on it, which is made possible by the inrush of air into the untreated lung, and this yielding of the inner wall of the cavity will in part neutralize the increased intrathoracic tension on the treated side. At the same time the partially collapsed lung will have occasion to expand less than if the inner wall were more rigid, and with the force of cohesion lost it is not in such good condition to expand as is the functionating lung. Because of its greater elasticity, the functionating lung will also yield more readily on expiration than will the partially collapsed lung, the mediastinum will move to that side and room will so be found for the gas cavity which will have its tension somewhat increased and pressure reduced by the greater tension of the sound pleura transmitted to it.

With the effect of inspiration and expiration on the gas in the pleural cavity partially neutralized by this swaying of the mediastinum, the pressures registered in the manometer will be less than if the full force of the expansion and contraction of the chest wall had obtained and the amplitude of movement of the fluid will consequently be less. (Note the especially small amplitude in Fig. 3.)

18. Bittorf: München. med. Wchnschr., June 7, 1910, No. 23, p. 1218.
19. Brauer: Beitr. z. path. Anat. u. z. allg. Path., 1905, Seventh Sup., p. 762.
20. Roth: Beitr. z. Klin. d. Tuberk., 1905, iv, 437.

When the mediastinum is rigid it will take less advantage of the relaxation of the diaphragm on the introduction of gas to yield to the opposing intrapleural tensions. On inspiration it will be but little modified in form, and will not, therefore, neutralize the effect of the enlargement of the pneumothorax cavity by the enlargement of the chest wall and the descent of the diaphragm. The respiratory movement will then more markedly influence the expansion of the collapsed lung, but simultaneously there will be more marked inspiratory and expiratory pressures recorded by the manometer. The amplitude will consequently be greater (contrast amplitude of B with C and D, Fig. 4). The amplitude in either case is, however, subject to modification in degree

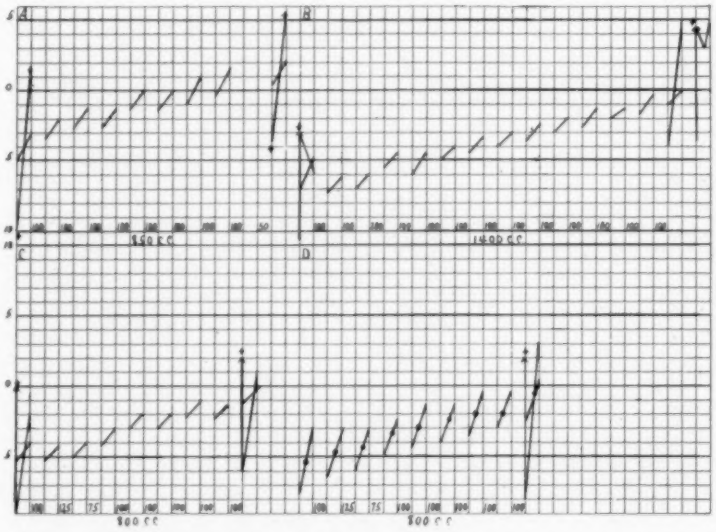


Fig. 3.—Case 1. Movable mediastinum (see Figs. 1 and 2). In this and the following figures amplitude is shown by length of line, the shorter lines quiet; the longer lines, deep breathing. Inspiration, the lower end; expiration the upper end. The circle on the amplitude line shows the mean pressure. + signifies that the level of the fluid is maintained when the breath is held. The arrow shows the phenomenon of rise of pressure at the end of inspiration. A, sixth refill, Aug. 12, 1914. Interval twenty-four days. Bore of needle 0.018 inch. Heart's impulse was originally 11 cm. to left of midsternal line; after refill, hyperresonance 5 cm. to right. B, seventeenth refill, May 27, 1915. Interval twenty-seven days. Same needle. Before refill, heart's impulse 12.5 cm. to left; after refill, dulness cannot be defined. C, fifteenth refill, April 3, 1915. Interval twenty-nine days. Same needle. Roentgenograms taken after this refill. Before refill, heart's impulse 7 cm. to left of midsternal line; after refill, dulness 7 cm. to right in fourth intercostal space. D, same refill. Large needle, bore, 0.042 inch, reading simultaneous with that of C.

because of varied conditions of breathing which best suit the patient's need at the moment. Emerson[16] has shown that the chest may assume different sizes on the introduction of fluid while the intrathoracic tension remains approximately the same, and that the respiratory oscillations are not in direct proportion to the respiratory movements, the efficiency of which bears an inverse relation to the degree of distention.

In either case, also, the pressures will be modified by the degree of expansion of the treated lung and some confusion in interpretation may be caused. As pointed out by Hamman and Sloan,[13] a reexpanded lung is shown by a very gradual rise in pressure on introducing each deciliter of gas, while a lung that remains collapsed is shown by a

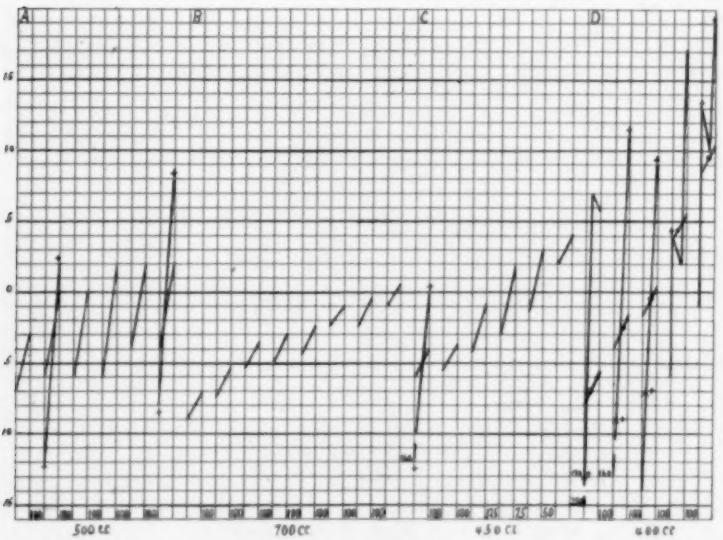


Fig. 4.—Case 2. Movable mediastinum becoming fixed. A, second refill, Sept. 23, 1914. Interval two days. Bore of needle, 0.035 inch. Heart's impulse displaced 3 cm. to left by refill. B, seventh refill, Dec. 8, 1914. Interval twenty-one days. Bore of needle, 0.018 inch. Heart's dulness displaced 5 cm. to left by refill; hyperresonance 3 cm. to left of midsternal line after refill. C, ninth refill, Jan. 30, 1915. Interval twenty days. Same needle. Heart's dulness before and after refill fixed at 2.5 cm. from position noted before beginning of pneumothorax. D, thirteenth refill, May 11, 1915. Interval twenty-eight days. Same needle. Heart's dulness fixed.

slow rise at first and then a very sudden and marked rise. The stationary points already mentioned, at which the pressure fails to rise following the introduction of one or two consecutive deciliters of gas help, we think, to distinguish such conditions. (See A, C, D, Fig. 3, and A and B, Fig. 4). They are points of emphasis in the curve char-

acteristic of the slow rise of pressure found when the mediastinum is movable. They may perhaps be explained by a somewhat irregular and momentarily more marked satisfaction of the elasticity of the functionating lung, the gradual satisfaction of which mainly accounts for the relatively slow rise in pressure, made possible by the further yielding of the mediastinum, partly the result of the continued relaxation of the diaphragm, rather than by an enlargement of the pleural space caused by the irregular enlargement of the thoracic wall, or than by an irregular collapse of the treated lung. We may surmise that the weak areas described by Nitsch play some part in their causation, as it is not unusual for hyperresonance to extend markedly to either side of the sternum even without a positive intrapleural pressure. High levels of the stationary points which may have been caused by bulging of such weak areas, were found in a case of very large pneumothorax with extreme movability of the mediastinum. At any rate, stationary points are found in consecutive refills to be more or less constant at some one, or at several levels in the pressure curves in cases in which the mediastinum is readily displaced, and are not found in those in which it is relatively fixed (Figs. 3 and 4).

The pressures for deep respiration, taken both at the beginning and the end of the refill, give information which is also suggestive and point to either condition, although the risk of rupture of the lung makes such deep breathing a dangerous experiment. With flexible mediastinum the amplitude for deep respiration is not disproportionate to that for quiet respiration (Figs. 3 and 4A) and is about the same at the end of the refill as at the beginnng. The incompletely collapsed lung no doubt plays a material part here as well as the yielding midwall. With rigid mediastinum, and especially if the rigidity of the pneumothorax wall is, so to speak, increased by a lung which does not readily reexpand, the amplitude may be quite disproportionate to that for quiet respiration, and extreme (Fig. 4) both at the beginning and at the end of the refill. There may also be material differences in the amplitude before and after the inflation depending on the recompression of the lung and on the muscular power that is brought to bear. When a rigid mediastinum obtains and the amplitude for forced respiration is relatively small, it is probable that there is considerable lung excursion which compensates the respiratory movements.

Needles of relatively small bore are, we think, better adapted for the estimation of varying amplitudes of movement of the water column than larger needles. With the latter the slowly rising curve and the stationary points can be well shown only by determining the mean pressure, after the manner adopted by Saugman, by means of a valve on the rubber connection between the limbs of the manometer, or, by a valve on the tubing to the manometer, as has been suggested by me.

The device recommended by v. Adelung[21] for making mean readings by means of a bypass might be modified so as to give a suitable standard caliber for noting oscillations, and this would make one independent of variations in the bore of different needles. The pressures recorded through a small needle will lie in the upper half of the amplitude recorded by a large needle, i. e., near the true mean pressure shown with a large needle (Fig. 3, C and D). Needles of a bore of 0.018 inch and 0.022 inch, B.W.G. Nos 26 and 24, have been used mainly. An amplitude of 2 cm. or less with a needle of 0.018 inch bore is suggestive of mediastinal displacement, and the more the excursion decreases or increases from this measurement the more or less suggestive it becomes.

We have also previously described a phenomenon, not infrequently found, which we have not seen mentioned elsewhere, but it is of some interest here. When the patient is asked to hold his breath at the end of inspiration the level of the fluid in the manometer suddenly rises several centimeters (Fig. 3, B, C, D; Fig. 4, D). At the end of the rise when he is asked to let out his breath there is a momentary drop in the level of fluid of about a centimeter; the pressure then rises again with continued expiration to a point dependent on conditions already described. The phenomenon was noted in six out of fifteen cases with large gas cavities, and in three out of fifteen cases with small gas cavities. It occurs with ordinary respiration as well as with forced respiration, is usually present both at the beginning and end of the seance, and it seems to be largely independent of the degree of pressure. It may be present at the initial and early operations and then disappear entirely or return some months later; also, when not present at first it may appear later (Figs. 3 and 4). It is present with both types of mediastinum. When this phenomenon was first noted it was confusing, as it was feared that a reexpanded lung had been pierced; but it was invariably noted that the pressure was maintained at the end of the rise and on expiration. The importance of the phenomenon is that it makes an exception to the rule that when the needle is in the pleural space the pressure is maintained on holding the breath at the end of inspiration.

One case (Case 1) with markedly movable mediatinum (Figs. 1 and 2) in which this phenomenon is present we had opportunity of examining with the fluoroscope, and a slight jerky rise of the diaphragm was noticed immediately on holding inspiration. This was seen both before and after a refill at which the beginning and ending mean pressures were —60 mm. and 0, respectively, and at which 1,400 cm. gas had been introduced. Eight roentgenograms taken of this patient's chest at different times failed to show diaphragmatic adhesions, though there was a lateral adhesion about the fourth rib. Three other cases

21. Von Adelung: Jour. Am. Med. Assn., 1913, lxi, 771.

in which it is present, with moderately large gas cavities and each having a fairly rigid mediastinum, showed on plates some diaphragmatic adhesions as well as lateral adhesions.

It is probable that this phenomenon is caused by a contraction of the lower ribs and abdominal muscles when the breath is held on inspiration, with a resulting increase of abdominal pressure and a passive rise of the relaxed diaphragm. With beginning expiration these muscles are first of all relaxed and this relaxation allows a momentary descent of the diaphragm with a resulting slight fall in intrathoracic pressure. Bittorf's[18] and Teske's[22] experiments and observations of paradoxical movements of the diaphragm are in accord with this explanation.

The practical application of these inferences may be seen from the following typical cases and accompanying charts:

CASE 1.—*Freely movable mediastinum.* (Figs. 1, 2 and 3.) No. 23, a woman. Collapse of left lung for hemorrhage recurrent over a period of five years. Left lung: disseminated fibroid disease throughout, not of intense character. Right lung: slight infiltration above third rib.

June 23, 1914. Initial reading (large-bore needle, 0.042-inch, No. 19 B. W. G.). —96 to —80 mm., deep respiration, —140 to —20, 200 c.c. air, ending middle pressure 0. A network of adhesions was present. The phenomenon was noted. A fairly large pneumothorax was readily obtained which ultimately required an average of 1,000 c.c. gas every three to four weeks. Breath sounds were almost completely suppressed after the inflation. After the fourth inflation there was no sense of pressure but the patient felt very tired for about a week after each refill. Dyspnea was felt after a mean positive pressure of 5 to 10 mm. Hyperresonance was 5 cm. to the right of the midsternal line. The apex beat, which before the initial inflation was felt 11 cm. to the left of the midsternal line, and which could usually be felt in almost the same position before a refill, became lost after one. Pulsation was occasionally seen after a refill 5 cm. to the right of the midsternal line, and relative cardiac dulness noted 5 to 7 cm. to the right. The characteristic curve of a movable mediastinum was early noted (Fig. 3), and has been consistently maintained. The deep respirations have never been disproportionate to those of quiet breathing and their relative values have always been consistently maintained. Because of this feature and the subjective symptoms, the mean pressure was reduced to 0, or a little less. This reduction lessened the sense of fatigue somewhat and the pulse, which had averaged 90, fell to a steady rate of 80 after two weeks. The sputum, small in amount, was but little influenced. The physical signs in the right upper lobe have diminished somewhat. The general condition of the patient has materially improved and apprehension has gone. Roentgenograms (Figs. 1 and 2), show a marked displacement of the heart after the refill which is materially more marked on expiration than on inspiration. There is a lateral adhesion seen about the fourth rib, but no diaphragmatic adhesion. The fluoroscope shows the greatest movement of the heart with respiration when there is a large amount of gas. The lung is not completely collapsed immediately after a refill. The yielding of the mediastinum, therefore, makes complete collapse a doubtful possibility or possible only at considerable risk. The phenomenon was present during the first five fillings and then disappeared until the ninth filling, since which time it has been usually present (Fig. 3, B, C, D). Through the fluoroscope the dia-

22. Teske: München. med. Wchnschr., Sept. 6, 1910, No. 36, p. 1892.

phragm was seen to rise in a jerky manner when the breath was held on inspiration.

CASE 2.—*Movable mediastinum becoming fixed.* (Fig. 4). No. 27, a woman. Right lung: collapsed for severe and long standing disease. Left lung: slight disseminated disease throughout upper lobe.

Sept. 21, 1914. Initial operation, adhesions present, 200 c.c. gas. Two days later gas was easily introduced, two sets of stationary points noted (Fig. 4, A), with the mean pressures at approximately —20 and —5 mm., large oscillations with large-bore needle, 0.035 inch, (B. W. G., No. 20). The further giving way of adhesions may account for these stationary points; gas 500 c.c.; apex beat shifts 2 cm.; no material difference between the extremes of deep inspiration and expiration at the beginning and end of the operation. Since the second inflation breath sounds immediately after the operation have been almost completely suppressed. By December 8, seventh refill, a large pneumothorax has been obtained. Hyperresonance extends 3 cm. to the left of the midsternal line; the left margin of relative cardiac dulness and the apex beat have each been displaced 4 cm. by the inflation. Curves with stationary points have been consistently seen. The rise is fairly slow; the oscillations rather irregular (B, Fig. 4). January 2. The rise in pressure for a smaller amount of gas, 500 c.c., is more abrupt and the oscillations are greater. Two days later the patient suffered great pain at the base of the left lung, which disappeared suddenly after four days. January 30, the rise in pressure is more rapid (C, Fig. 4), from —50 to +30 mm. by 450 c.c. gas. No stationary points are noted; the oscillations are materially larger but variable; suggestion of fluid in the needle; the excursion on deep respiration has greatly increased. The relative cardiac dulness is fixed at 8.5 cm. to left of the midsternal line both before and after the inflation. The characteristics of a fixed mediastinum are now seen, and these continue. The succussion sign of fluid was obtained after the tenth refill, but was not found again. At the twelfth refill the deep respiratory excursion became enormous, showing an amplitude of 230 and 220 mm. before and after the inflation (D, Fig. 4). The phenomenon was first seen at the end of this inflation but has since been constant. It is well illustrated in the chart (Fig. 4). Since the mediastinum has become fixed the pressures have been consistently raised so that now the ending mean pressure is 90 mm. The patient is more comfortable, with almost entire absence of expectoration, and physically better than at any time since the pneumothorax was induced.

The first case illustrates the correlation between fatigue symptoms, physical signs of displacement of the mediastinum and the data here given for inferring a movable mediastinum from the readings of the manometer. Relief from the symptoms was obtained by reducing the pressure to just below zero. The second case required care in the adjustment of pressure for both the functionating lung and heart. Restraint was exercised in the pressure used and frequent refills were undertaken until the readily displaced mediastinum became fixed, following the pleurisy, which fixation is well shown by the manometer. It then proved to be beneficial to increase the pressure and after this the intervals could be lengthened. A number of other cases might be cited to show the correlation between physical signs and the manometric indications of mediastinal displacement. In some cases in which the physical signs of displacement failed or were less marked, the manometer has proved a distinct help in estimating the condition of the mediastinum.

SINO-AURICULAR BLOCK DUE TO TOBACCO POISONING*

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Sino-auricular block—standstill of the entire heart—is a rare type of arhythmia in the adult. It is usually the result of digitalis poisoning.[1] Recently, however, a case due to salicylic acid has been described.[2] It has occasionally been induced by vagal pressure[3] in patients with normal rhythm and with paroxysmal tachycardia[4] and has frequently been induced experimentally.[5] The report of its occurrence as a clinical condition with accompanying graphic proof is exceedingly rare.[5, 6].

It has long been known that overindulgence in tobacco causes arhythmias, but their type has not been sufficiency studied by graphic methods to determine their exact nature. I have observed several cases of extrasystoles (usually auricular), one case of auricular flutter and one of auricular fibrillation due to tobacco poisoning. As sino-auricular block has never been ascribed to this cause, the following two cases seem sufficiently noteworthy to warrant publication.

CASE 1.—E. I. H., aged 28, architect, married six years, has two children. He was always athletic. When 6 years old he had diphtheria with tracheotomy; otherwise he has had no serious illness. At 15 he began smoking and has been smoking uninterruptedly since, his usual quota being three cigars and three pipefuls daily; never cigarets. His pulse irregularity was first noticed when examined for admission to the army at the age of 20. His arhythmia does not annoy him or in any wise interfere with his work or exercise. There was no dyspnea on exertion and the arhythmia was not affected by exercise. There was no precordial pain or decompensation. The systolic blood pressure was 150 mm., the diastolic, 70 mm. There was a vigorous apical impulse and the cardiac sounds were normal. Orthodiascopic examination showed slight left ventricular enlargement. The urine showed no abnormalities, and examination of the abdominal organs and the nervous system revealed nothing of note. The heart contracted regularly at the rate of about 100 per minute for two, three, or four beats and then there was a sudden pause during which no sound was heard at the apex nor any pulse beat felt at the wrist. Examination of the

* Submitted for publication, Jan. 3, 1916.

1. Hewlett: Jour. Am. Med. Assn., 1907, lvii, 47. Rihl: Deutsch. Arch. f. klin. Med., 1908, xciv, 286. Cohn and Fraser: Seventeenth International Congress of Medicine, 1913, Section 6, Medicine.
2. Sicard and Meara: Am. Jour. Med. Sc., 1915, cl, 843.
3. Robinson and Draper: Jour. Exper. Med., 1911, xiv, 217. Von Hoesselin: Deutsch. Arch. f. klin. Med., 1914, cxiii, 537.
4. Cohn and Fraser: Heart, 1913-14, v, 93.
5. Eyster and Evans: THE ARCHIVES INT. MED., 1915, xvi, 832.
6. Lewis: Clinical Electrocardiography, p. 100.

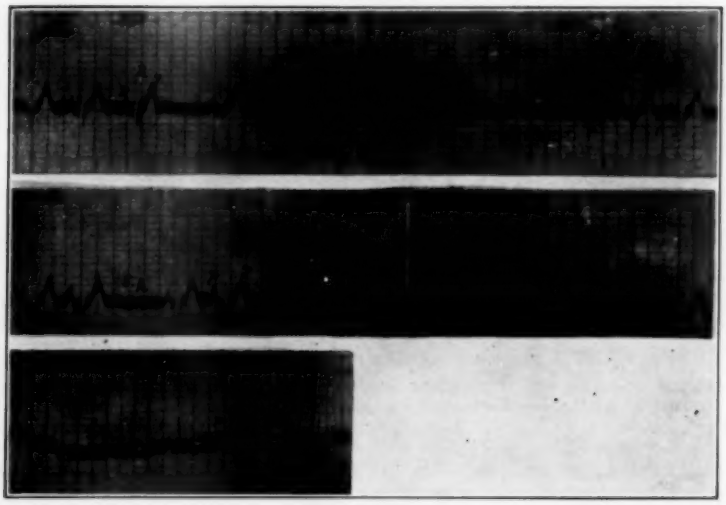

Figure 1

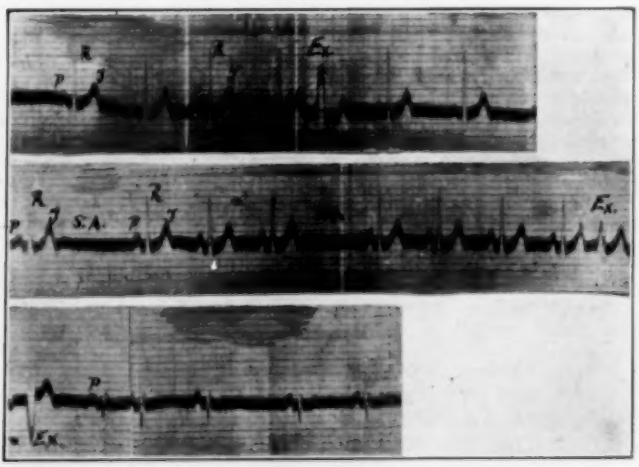

Figure 2

Figure 1.—Electrocardiogram from Case 1. In this figure and Figure 2 the vertical lines measure one-fifth second; the different leads are marked 1, 2, 3; P = the auricular, R-T, the ventricular complex. S.A. = sino-auricular block, Ex = ventricular extrasystole.

electrocardiogram (Fig. 1) showed sino-auricular block, a sudden arrest of the whole heart (S. A., Fig. 1). The length of most of the pauses was somewhat less than two normal beats, a condition ordinarily found in this type of arhythmia. The patient refused to stop smoking; the arhythmia continued. This case was uncomplicated by any evidence of organic cardiovascular disease.

CASE 2.—A. B., physician, aged 57; always led a very active life; had been a heavy and constant cigaret smoker since youth, averaging thirty cigarets daily. Several years ago he was treated medically for duodenal ulcer and has had no symptoms since. During the last eight years he has complained of some dyspnea. In addition, for the last two or three years he has had occasional attacks of precordial pain. For several months both symptoms have become worse. His pulse irregularity began eight months ago. The patient was somewhat stout; his color pasty gray. The average systolic blood pressure was 150 mm.; the diastolic, 100 mm. There was no pain on precordial pressure. Except for a faint systolic murmur at the right base, the heart sounds were normal. The orthodiascope showed that the aortic arch and left ventricle were somewhat enlarged. The neurological status was normal. There was slight edema of the legs. On one examination the urine contained a few hyaline casts and a slight trace of albumin. Extrasystoles were heard at the apex and transmitted to the wrist about once in every three or four beats; their number decreased after exercise. Besides the extrasystoles, there were occasional complete pauses of the heart and pulse; the electrocardiogram (Fig. 2, lead 2, S. A.) showed that the pauses were due to sino-auricular block and almost equalled two normal contractions. Ventricular extrasystoles (Fig. 2) were seen in the different leads. The ventricular rate, when rhythmical, was about 80 per minute; the conduction time (P-R interval), normal. The patient was advised to stop smoking and moderate doses of bromids were prescribed. The sino-auricular block disappeared within three days and has not since returned. The extrasystoles also disappeared for a few days, but then recurred about once every minute; after two weeks they were as frequent as at the first examination. With their return, precordial pains and dyspnea increased. Digipuratum tablets, three daily, and theobromin sodium salicylate, with Karrel diet, once weekly, were prescribed, and the patient's work was somewhat restricted. Within three weeks, the extrasystoles, precordial distress and dyspnea entirely disappeared. Except for occasional ventricular extrasystoles following extreme effort, the patient feels quite comfortable.

A study of the history and clinical course showed that the two distinct types of arhythmia, sino-auricular block and ventricular extrasystoles, were apparently caused by two different factors, the former by tobacco, the latter probably by myocarditis and nephritis. The sino-auricular block disappeared very soon after smoking was stopped; the extrasystoles, only when compensation was fully restored. Ventricular extrasystoles are known to accompany any type of cardiovascular disease with decompensation. With restoration of compensation they usually disappear, a result that was accomplished in this case.

COMMENT

Sino-auricular block is commonly ascribed to a vagus influence acting on the sinus region of the heart in which lies the pacemaker (the sino-auricular node) with its rich nerve plexuses and ganglia; morbid vagus influences may block out an entire sequential auriculo-

ventricular contraction and produce a corresponding pause of cardiac activity. In animals the experimental effects on the heart and aorta of nicotin injections and of tobacco inhalations and their possible correlation with similar cardiovascular disease in man are still disputed questions and have no bearing on the subject matter of this paper. These observations, however, have tended to minimize the definitely known poisonous effects of nicotin on nerves and nerve endings. Langley and Sherrington[7] were among the first to demonstrate the neurotropic effects of nicotin, the most active of the tobacco alkaloids. Pezzi and Clerc[8] studied the effects of nicotin injections upon cardiac rhythm and divided these into an initial bradycardial, and a later tachycardial, phase. In the former, they occasionally noted auricular arrest with ventricular arhythmia, and less frequently auricular fibrillation; with the tachycardia, they observed lessened auriculoventricular conduction time, retrograde conduction, auricular extrasystoles or incomplete auriculoventricular dissociation. Cushny[9] showed that experimental nicotin injections disturbed normal cardiac rhythm mainly by a morbid neurotropic influence acting on the ganglionic terminations of the vagus and sympathetic nerves; thus it seemed possible to have two opposite effects on heart rate—abnormal slowing or acceleration—apparently depending on the preponderant selective action for vagus or accelerator nerve endings. That such action may rapidly shift from one to the other seems plausible from our present scanty clinical knowledge that nerve tone may be a very unstable quality, at times readily influenced.

The clinical cases here reported seem to substantiate, in a degree, the results of animal experimentation. In Case 2, the extrasystoles were the result of decompensation. The sino-auricular block represented the effects of nicotin poisoning on the vagus alone. Patient 1 had no organic disease. The moderate acceleration interspersed with irregularly occurring sino-auricular block was apparently a clinical prototype of the two opposed experimental effects of the tobacco alkaloid on the vagus and accelerator.

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7. Langley and Sherrington: Jour. Physiol., 1891, xii, 43.
8. Pezzi and Clerc: Jour. de physiol. et path. gén., 1913, xv, 1.
9. Cushny: Pharmacology and Therapeutics of the Action of Drugs, 1913, p. 272.

OBSERVATIONS ON THE TYPHOIDIN REACTION*

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In every community in which typhoid fever is endemic, the desire exists for a method of determining the presence or absence of immunity to the disease.

A test that could be relied on to furnish an index of resistance to invasion by the typhoid bacillus, would determine the need of prophylactic vaccination or revaccination, and in certain less common instances, perhaps afford the means of identifying a previous obscure infection as typhoid fever. The shortcomings of the ordinary immunological procedures for this purpose, long recognized, were emphasized anew by Gay and his co-workers, who devised the typhoidin reaction to supplement them.

Gay and Force[1] prepared an extract of the typhoid bacillus according to the technic employed by Koch in the preparation of "Original Tuberculin;" 250 c.c. of 5 per cent. glycerin broth were inoculated with a strain of *Bacillus typhosus* (Dorset Army Strain No. 5), and incubated for five days. The culture was then reduced without filtration to one-tenth of its original volume by evaporation over an acetone bath at 56 C. for about eight hours. The end product they named "typhoidin."

For control tests, 5 per cent. glycerin broth was concentrated at the same time and by the same means to an equivalent volume.

The method of carrying out the original tests was essentially that utilized by von Pirquet in eliciting the cutaneous tuberculin reaction. It consisted in producing an abrasion of the skin, of uniform size and depth, designed to cut just through the epidermis of the arm without drawing blood. The abrasion was produced by making a twist of a chisel with a straight edge, 2.25 mm. wide, with square corners, and tempered to resist sterilization by burning alcohol. The skin was cleansed with 95 per cent. alcohol. Two uniform abrasions were made on the upper arm or forearm, and with a sterile toothpick the control solution was rubbed into the inner spot and the typhoidin solution was applied to the outer one. The reactions were observed six and twenty-

* Submitted for publication, March 13, 1916.
* From the Medical Clinic of the Johns Hopkins Hospital.
1. Gay, F. P., and Force, J. N.: THE ARCHIVES INT. MED., 1914, xiii, 471.

four hours later, and rarely at subsequent periods. In a few instances an accelerated response was noted after six hours, but this subsided within twenty-four hours. Not infrequently a positive reaction persisted for a week. Generally, the control spot showed a healed abrasion 2 mm. in diameter, not surrounded by an areola. In fewer instances, a slight zone of traumatic redness was seen about the abrasion. In the latter group, when there was a positive reaction about the typhoidin spot, the difference between its areola and the redness about the control spot was readily measured. As evidence of a positive reaction, a difference of 2.5 mm. between the two areolas was arbitrarily chosen. The positive spot measured from 4 to 12 mm. in diameter, was usually somewhat indurated and often clearly demarcated. In negative cases the same response was noted in the control and in the typhoidin spot.

The results of the application of this test by Gay and Force may be briefly summarized:

Of 21 cases with a definite history of typhoid fever from four and a half months to four years previously, 20 gave a positive reaction.

Of 6 cases with a history suggesting typhoid fever in the past, 6 gave a positive test.

Of 41 negative control cases, 35 gave negative tests and the remaining 6 "may be suspected of having had a mild and undiagnosed attack of typhoid fever."

Of 15 individuals vaccinated with Army vaccine, eight months to four and three-fourths years previously, 9 reacted positively.

Twenty-five individuals vaccinated with the sensitized vaccine of Gay and Claypole one to eight months before the test, all developed a positive reaction.

In a later communication, Gay and Claypole[2] reported the results of the typhoidin test made with a modified test preparation injected intradermically.

Original typhoidin solution was precipitated with twenty volumes of alcohol, filtered, and the filtrate, after being washed with absolute alcohol and ether, was dried on porcelain plates in a vacuum over sulphuric acid. The control 50 per cent. glycerin broth was similarly treated. For the tests a small amount of each sediment was dissolved in phenolated saline solution equivalent to the original volume of concentrated typhoidin or even to a double concentrated solution. Such solutions when kept in a cool place gave a reaction in typhoid immunes for at least a month.

The exact amount of typhoidin used in carrying out the intradermic test is not mentioned. The only statement as to the quantity of the

2. Gay, F. P., and Claypole, E. J.: THE ARCHIVES INT. MED., 1914, xiv, 671.

preparation employed is that "the tests were applied by making blebs, one on each upper arm."

The results of the typhoidin skin test summarized in this communication indicated that 95 per cent. (40 of 42) individuals with a history of having had typhoid fever gave positive reactions, and that of control persons with no history of the disease 86 per cent. (38 of 44) gave negative reactions. Further, of 6 persons reacting positively, 5 probably had had abortive typhoid fever.

Gay and Claypole found that individuals immunized with typhoid vaccine "reacted in the majority of cases for about two years and then became more frequently negative," and inclined to the view that "a negative skin test at least a month after vaccination indicated the need of revaccination."

The evidence that a positive skin test with typhoidin indicated immunity to typhoid fever was further supported by similar reactions induced in immunized rabbits.

The studies of Gay and Force and of Gay and Claypole seemed to show that a satisfactory gage of resistance to infection with the typhoid bacillus had been found.

Nichols[3] carried out both the dermal and the intradermal tests of Gay. The former reaction yielded disappointing results, due, he thought, to the deterioration of the typhoidin solution. The reactions made with the precipitated preparation gave positive results in 75 per cent. of persons who had had typhoid fever, and in 64 per cent. of fifty persons who had never had typhoid fever but who had received prophylactic vaccine within four years.

Pulay[4] published the results of a series of tests carried out on one hundred thirteen persons, some of whom had had typhoid fever recently or some time before, some of whom had received antityphoid vaccine, and others of whom gave a negative history. Apparently, his findings confirm those of Gay and Force and of Gay and Claypole.

The need for such a test in the medical department of the Johns Hopkins University and Hospital has long been recognized. The large student body, the corps of nurses, the staff, the majority of whom receive prophylactic vaccination against typhoid fever, constitute a group the resistance of which to infection with the *Bacillus typhosus* it is expedient to know. Accordingly, the following observations were made:

In order to make the results of these observations as nearly comparable as possible, the typhoidin was prepared strictly according to

3. Nichols, H. J.: Jour. Exper. Med., 1915, xxii, 780.

4. Pulay, E.: Wien. klin. Wchnschr., 1915, xxviii. The original article was not to be obtained. The quoted data were contained in an abstract in Jour. Am. Med. Assn., 1916, lxvi, 230.

the technic of Gay, and, for the sake of emphasis, it is again detailed: Two hundred fifty cubic centimeters of 5 per cent. glycerin broth were inoculated with *Bacillus typhosus* (Army Strain "Rawlings") and incubated for five days at 37 C. The culture was then evaporated at 56 C. without filtration to one-tenth of its original volume, and precipitated with ten volumes of absolute alcohol. The precipitate, washed with absolute alcohol and ether, was then desiccated in a vacuum over calcium chlorid.

The control preparation was prepared by treating uninoculated sterile 5 per cent. glycerin broth in the same way. The end product in each instance was a slightly tinted white cake which, when ground in a mortar, yielded a fine white powder readily soluble in water or in salt solution.

No cutaneous tests were made. In each case a known weighed quantity of the typhoidin, dissolved in a constant volume of 0.85 per cent. salt solution, was injected into the skin of the upper arm or forearm after it had been cleaned with alcohol. At the time of the injection of the typhoidin solution, an injection of an equal amount of the control solution was given. The results of the inoculations were noted immediately, after six hours, twenty-four hours, and often at daily intervals for a week.

In the major part of the series to be recorded, a polyvalent typhoidin was used. This was prepared according to the described technic, but the end product represented the combined precipitates of cultures of thirty-five strains of the typhoid bacillus.

In carrying out the tests from 0.00001 to 0.02 gm. of typhoidin was used. The solution of typhoidin was made in 0.85 per cent. salt solution and was injected within two hours of its preparation.

Within a few minutes to half an hour after the injection, an erythema 0.5 to 2.0 cm. in diameter developed, in the center of which there was usually a small area of edema. During the next few hours the erythema continued to spread and the central edema subsided, leaving at the site of the injection a slightly elevated indurated nodule, the skin over which was darker than the surrounding area.

When small doses, such as 0.00005 gm. or less, of typhoidin were used, the reaction was purely local and reached its maximum within twenty-four hours, when there was generally a small, broad nodule at the site of the puncture. This was surrounded by a zone of erythema that varied in size but was rarely greater than 5 or 6 cm. in diameter. The color faded during the next twenty-four hours, leaving a small central stain that at times persisted several days or even a week.

When larger amounts of typhoidin were injected, the resultant reaction was similar but of greater extent. In addition, any or all

of the following signs occasionally developed: Marked local tenderness, heat and swelling; pain when the elbow was flexed; lymphangitis, axillary lymphadenitis; even slight fever and malaise.

Occasionally the erythema was sharply demarcated, but more often it was diffuse and its outlines so difficult to discern that accurate measurements of its extent could not be made. This was especially true of the superior margin, for the erythema often extended up the arm in a gradually fading band.

A reaction following the intradermic injection of solutions containing less than 0.0001 gm. of the precipitate from the uninoculated broth was usually lacking. In those instances in which larger amounts were used, a small zone of slight erythema resulted.

RESULTS OF THE TESTS

A. INDIVIDUALS WITH A RELIABLE HISTORY OF TYPHOID FEVER

The test was carried out in ten individuals who had had typhoid fever. The time that had elapsed since the infection, the amount of typhoidin injected, and the reaction elicited, are summarized in Table 1.

TABLE 1.—TYPHOIDIN TEST OF INDIVIDUALS WHO HAD HAD TYPHOID FEVER

Name	History	Typhoidin, Mg.	Reaction 24 Hours		Name	History	Typhoidin, Mg.	Reaction 24 Hours	
			Test Cm.	Control Cm.				Test Cm.	Control Cm.
I.	Typhoid fever 10 yrs. ago	1/4	6 × 10	.....	H.	No typhoid or vaccine	1/4	7 × 11	.....
P.	Typhoid fever T° normal 1 mo.	1/4	10 × 15	.....	P.	No typhoid or vaccine	1/4	6 × 10	.....
S.	Typhoid fever T° normal 1 mo.	1/10	4 × 8	1 × 1	M.	No typhoid or vaccine	1/10	5 × 5	1 × 1
W.	Typhoid fever T° normal 1 mo.	1/10	4 × 8	N. P.	H.	No typhoid or vaccine	1/10	3 × 6	N. P.
F.	Typhoid fever T° normal 1 mo.	1/10	4 × 6	N. P.					
M.	Typhoid fever 10 yrs. ago	1/20	4 × 5	0.5 × 0.5	H.	No typhoid or vaccine	1/20	5.5 × 10	0.5 × 0.5
P.	Typhoid fever 8 yrs. ago	1/20	6 × 8	0.5 × 0.5	N.	No typhoid or vaccine	1/20	3.5 × 6	N. P.
H.	Typhoid fever 12 yrs. ago	1/20	3 × 2.5	N. P.	A	No typhoid or vaccine	1/20	3 × 4.5	N. P.
R.	Typhoid fever 15 yrs. ago	1/40	5.5 × 11	N. P.	H.	No typhoid or vaccine	1/40	4 × 9	N. P.
					C.	No typhoid or vaccine	1/40	3.5 × 4	N. P.
B.	Typhoid fever 6 mos. ago	1/100	2 × 2.5	N. P.	J.	No typhoid or vaccine	1/100	3 × 4.5	N. P.

N. P. = needle puncture.

Accepting as the criterion of a positive reaction a difference of 2.5 mm. in diameter between the areola resulting about the site of the injection of the typhoidin and that developing around the injection site of the control preparation, all ten of these individuals gave a positive reaction; but an identical procedure carried out in ten persons who had never had typhoid fever, any illness that was probably abortive typhoid fever, or a prophylactic typhoid vaccination, showed a similar result.

TABLE 2.—Typhoidin Tests of Individuals Who Had Received Prophylactic Antityphoid Vaccination and of Those Who Had Not Had Antityphoid Vaccination or Typhoid Fever

Name	History	Typhoidin, Mg.	Reaction 24 Hours		Name	History	Typhoidin, Mg.	Reaction 24 Hours	
			Test Cm.	Control Cm.				Test Cm.	Control Cm.
G.	Vaccine 1½ yrs. ago	1/4	6 × 10	.....	A.	No typhoid fever or vaccine	1/4	6 × 12	.....
M.	Vaccine 4 mos. ago	1/4	7 × 14	.....	H.	No typhoid fever or vaccine	1/4	5 × 12	.....
B.	Vaccine 6 mos. ago and 3 yrs. ago	1/4	6 × 8	.....					
S.	Vaccine 1½ yrs. ago	1/10	5 × 10	0.5 × 0.5	T.	No typhoid fever or vaccine	1/10	5 × 10	2 × 1
J.	Vaccine 1 yr. ago and 3 yrs. ago	1/10	5 × 10	0.5 × 0.5	C.	No typhoid fever or vaccine	1/10	4 × 6	N. P.
M.	Vaccine 2 mos. ago	1/10	5 × 9	N. P.*	R.	No typhoid fever or vaccine	1/10	6 × 11	N. P.
H.	Vaccine 3 mos. ago and 3 yrs. ago	1/10	3.5 × 4	N. P.					
K.	Vaccine 8 mos. ago	1/10	5 × 10	0.5 × 0.5					
W.	Vaccine 3 yrs. ago	1/20	3 × 6	1 × 1	A.	No typhoid fever or vaccine	1/20	3 × 4.5	N. P.
A.	Vaccine 2 yrs. ago	1/20	3 × 5	0.5 × 0.5	H.	No typhoid fever or vaccine	1/20	5.5 × 10	0.5 × 0.5
M.	Vaccine 2 yrs. ago	1/20	2 × 4	0.5 × 0.5	M.	No typhoid fever or vaccine	1/20	4.5 × 6	N. P.
S.	Vaccine 3 yrs. ago	1/20	3 × 2.5	0.5 × 0.5					
L.	Vaccine ½ yr. ago	1/20	2 × 2	N. P.					
B.	Vaccine three courses in past 4 yrs.	1/20	4 × 6	0.5 × 0.5					
M.	Vaccine 2½ yrs. ago	1/20	4.5 × 9	N. P.	L.	No typhoid fever or vaccine	1/20	3 × 5	N. P.
S.	Vaccine 1½ yrs. ago and 3½ yrs. ago	1/20	4.5 × 9	N. P.	J.	No typhoid fever or vaccine	1/20	3 × 6	N. P.
T.	Vaccine 2 yrs. ago	1/20	5 × 10	N. P.	P.	No typhoid fever or vaccine	1/20	5 × 7	N. P.
T.	Vaccine 2½ yrs. ago	1/20	3.5 × 6	N. P.					
C.	Vaccine 1½ yrs. ago and 3 yrs. ago	1/20	5 × 6.5	N. P.					
H.	Vaccine 1 yr. ago and 3½ yrs. ago	1/20	3.5 × 6	N. P.					
H.	Vaccine 2 yrs. ago and 4 yrs. ago	1/40	4 × 7	N. P.	W.	No typhoid fever or vaccine	1/40	2 × 4.5	N. P.
W.	Vaccine 3½ yrs. ago	1/40	3.5 × 5	N. P.	T.	No typhoid fever or vaccine	1/40	2.5 × 6.5	N. P.
P.	Vaccine 6 mos. ago	1/40	3 × 4	N. P.	P.	No typhoid fever or vaccine	1/40	2 × 1.5	N. P.
D.	Vaccine 3 yrs. ago	1/40	2 × 7	N. P.					
R.	Vaccine 18 mos. ago and 3 yrs. ago	1/40	3 × 3	N. P.					
M.	Vaccine 6 mos. ago	1/40	4 × 5	N. P.					
S.	Vaccine 4 mos. ago and 4 yrs. ago	1/100	2 × 4	N. P.	G.	No typhoid fever or vaccine	1/100	3 × 4.5	N. P.
C.	Vaccine 8 mos. ago and 2 yrs. ago	1/100	1.5 × 2	N. P.	B.	No typhoid fever or vaccine	1/100	1.5 × 3	N. P.
					K.	No typhoid fever or vaccine	1/100	3 × 4	N. P.
					B.	No typhoid fever or vaccine	1/100	1.8 × 2.5	N. P.

N. P. = needle puncture.

B. INDIVIDUALS WHO HAD RECEIVED PROPHYLACTIC ANTITYPHOID VACCINATION

Twenty-eight medical students and physicians, who had received one or more courses of injections of typhoid vaccine three months to five years ago, were each given an intradermic injection of typhoidin solution. The dosage used and the extent of the reaction that followed are seen in Table 2.

These results again show in all cases the chosen criterion of a positive reaction. But as in Series A, so in this series, a comparison of these tests with those obtained in normal controls who had never had typhoid fever, any illness that suggested typhoid fever or antityphoid vaccination, shows identical findings.

C. INDIVIDUALS WHO HAD NOT HAD TYPHOID FEVER OR PROPHYLACTIC ANTITYPHOID VACCINATION

The test was carried out in twenty-five such people, and the results have been recorded in Tables 1 and 2. These findings need little comment. It is not likely that more than a small percentage of these individuals could have had an unrecognized attack of typhoid fever, and even more improbable that any large proportion of them possessed a natural immunity to the disease.

CONCLUSION

The typhoidin reaction carried out in sixty-six individuals failed to furnish data by means of which it was possible to differentiate between those who had neither had typhoid fever nor received prophylactic vaccination and those who had either had the disease or had been artificially immunized against it.

STUDIES OF THE HEART'S FUNCTIONAL CAPACITY AS ESTIMATED BY THE CIRCULATORY REACTION TO GRADUATED WORK*

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The method used in these studies to determine the heart's functional capacity consisted briefly in the deductions made from frequent measurements of the pulse and systolic blood pressure after increasing amounts of work as described in a former article.[1] When the highest blood pressure was noted immediately after work and then quickly subsided this work was considered to have been within the heart's capacity. When, on the other hand, the highest pressure was reached a minute or two after the completion of work, at a time when the pulse had dropped back towards normal, that work was regarded as having overtaxed the heart.

Graduated work was furnished in a few experiments by a bicycle ergometer of the type described by Krogh and Linhard,[2] but in the majority of cases by movements of flexion, extension and swinging with iron dumb-bells weighing from 3 to 20 pounds each.

Dumb-bells afford a most practical means of furnishing graduated work either for testing the heart's functional capacity or for the treatment of patients convalescing from cardiac insufficiency. Computation of the amount of work performed through dumb-bell exercises is, however, not absolute, as will be seen from the following examples: If a 5-pound dumb-bell is extended upward from the shoulder through 2 feet, 10 foot-pounds of work is performed with each extension. With a 10-pound bell 20 foot-pounds, or twice as much work, would be performed in the same space of time. Yet these figures do not represent the entire amount done, as two sources of work have been ignored.

During the time consumed in the exercise the bell is being supported near the shoulder, which entails muscular effort. Also when the bell returns to the shoulder some force is exerted to prevent too rapid a fall. Considerable additional work which cannot be estimated in foot-pounds is performed in these ways. The actual work done

* Submitted for publication, March 2, 1916.
* From the Medical Service of the House of Relief.
1. Barringer, T. B., Jr.: THE ARCHIVES INT. MED., 1916, xvii, 363.
2. Krogh and Lindhard: Skandinavisches Arch. f. Physiol., 1913, xxx, 378.

by the extension or flexion of dumb-bells is therefore the sum of three parts. The first, which arises from moving the bell through a certain distance, we can measure; the second, arising from supporting the bell, and the third, derived from muscular resistance, we cannot measure. Although this limitation makes our estimations relative and not absolute, it does not invalidate comparisons of the heart's efficiency obtained by means of this measurable component of dumb-bell work. An idea of the number of foot-pounds which elude computation in this way may be gained by a consideration of the heart's capacity as calculated absolutely through work on the bicycle ergometer.

A laboratory assistant, aged 23 years, with a normal heart, and in fair physical training, was able to do 8,700 foot-pounds per minute for five minutes on the bicycle ergometer without overtaxing his heart. Working at the rate of 8,900 foot-pounds per minute, however, in two minutes he had overtaxed his heart. Another assistant, aged 21 years, with a normal heart, but with not quite as powerful a physique as the first man, was able to do 7,200 foot-pounds per minute for four minutes on the ergometer. At the rate of 9,900 foot-pounds per minute his heart's capacity was exceeded in two and a half minutes. For comparison the cardiac efficiencies of two young men, a few years older, with normal hearts and in fair training, were determined by graduated work with dumb-bells. One was able to do 9,600 foot-pounds in sixty seconds, but working at the same rate for ninety seconds his heart was overtaxed. The other man did 7,600 foot-pounds in sixty seconds, but was unable to continue at this rate for ninety seconds without exceeding his heart's capacity.

Again, a patient convalescing from cardiac insufficiency was able to do 1,300 foot-pounds per minute on the ergometer for two and a half minutes with normal circulatory reaction. The same day 1,200 foot-pounds of dumb-bell work in sixty seconds overtaxed his heart.

The disparity thus shown between the values obtained in these experiments with the ergometer and those obtained from dumb-bell exercise is large and must represent that part of dumb-bell work which we cannot translate into work units.

In the light of the preceding explanation it is clear, we trust, that the values stated in the subsequent studies of the heart's efficiency as determined by graduated dumb-bell work are all considerably lower than they should be and yet they afford a fairly accurate means of comparison.

Table 1 represents the functional capacities of the hearts of normal persons as determined by graduated dumb-bell work and by the ergometer.

TABLE 1.—Functional Capacities of Normal Hearts as Estimated by Graduated Work with Dumb-Bells and with the Bicycle Ergometer

DUMB-BELL WORK

Case	Name	Age	Sex	Number of Foot-Pounds for Which Heart Can Supply Blood to Muscles	No. of Foot-Pounds by Which Heart is Overtaxed to Supply Blood to Musc.
1	B.	56	♀	1700 in 30 sec.	2000 in 30 sec.
2	R.	39	♀	2200 in 60 sec.	2600 in 30 sec.
3	D. H.	23	♀	4500 in 60 sec.	4800 in 60 sec.
4	H.	45	♂	2600 in 45 sec.	3000 in 45 sec.
5	T. H.	40	♂	8200 in 60 sec.	11000 in 60 sec.
6	B.	37	♂	7000 in 60 sec.	8600 in 60 sec.
7	E.	44	♂	6800 in 60 sec.	7800 in 60 sec.
8	V.	26	♂	9600 in 60 sec.	10000 in 60 sec.
			ERGOMETER		
9	S.	23	♂	43500 in 5 min.	17800 in 2 min.
10	M.	21	♂	28800 in 4 min.	24800 in 2½ min.

A comparison between Cases 1 and 3 is interesting. Patient 1 was a woman, aged 56, who had never taken any more vigorous exercise than an occasional walk. Patient 3 was a woman 23 years old, in excellent physical condition, who played tennis and swam occasionally.

Patient 4 was a professional man, aged 45, who had taken practically no vigorous physical exercise since boyhood, because when he did so he became short of breath and felt exhausted afterwards. His heart was apparently normal in every respect, but his cardiac capacity was the lowest of twenty normal men of middle age. By a course of graduated exercise his heart's efficiency was increased so that he could do 6,400 foot-pounds in sixty seconds, instead of 2,600 foot-pounds in forty-five seconds which was his initial capacity.

Three cases have been selected to illustrate the course of the heart's functional capacity in patients suffering from varying degrees of decompensation. The first patient, J. C., a watchman, 54 years old, had had his first attack of cardiac insufficiency in 1913, having at that time swelling of the feet and legs, and shortness of breath. On Sept. 8, 1915, he was admitted to the House of Relief complaining of the same symptoms. He was a thin man with gray hair, dyspneic, and with markedly swollen legs and scrotum. The heart was enlarged and showed an aortic and mitral regurgitation. There were signs of small quantities of fluid in both pleural cavities. The liver was decidedly enlarged, and the blood showed a ++++ Wassermann reaction. He

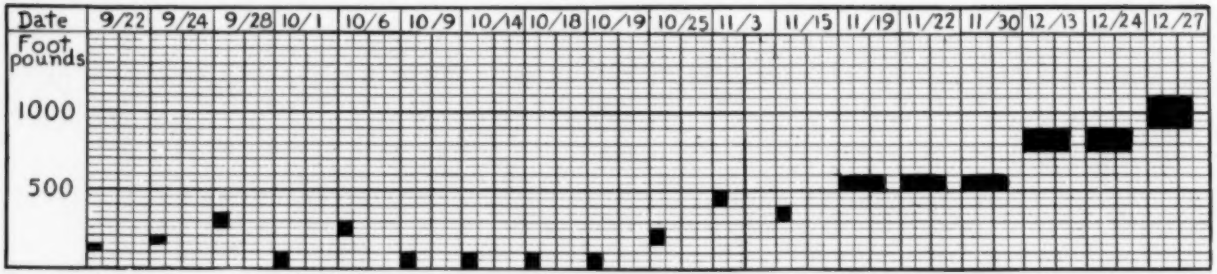

Chart 1.—Course of the heart's capacity in J. C., suffering from aortic regurgitation and cardiac insufficiency. In this and the following charts each space between two consecutive perpendicular lines represents 15 seconds. The black squares represent the heart's capacity. For illustration, on September 22, the heart, without being overtaxed, was able to supply sufficient blood to the muscles to enable them to do 100 foot-pounds in 15 seconds. The performance of 150 foot-pounds in 15 seconds overtaxed the heart. So the capacity is represented by the black square lying between 100 and 150 foot-pounds.

received altogether 16 drams of tincture of digitalis and twenty intramuscular injections of salicylate of mercury. September 22, the cardiac capacity was tested and the patient was given a course of graduated exercise. A few days after the exercise began the digitalis was stopped. Chart 1 represents the course of the heart's functional capacity.

September 22, when he was able to walk slowly around the ward for a short distance, his cardiac capacity was very low. On December 27, when his capacity had increased to between 900 and 1,100 foot-pounds performed in 60 seconds, he was much stronger and able to do light work.

The second patient, C. G., was a salesman, aged 31 years, who had had four attacks of acute rheumatic fever. For two years he had had occasionally symptoms of cardiac insufficiency, but for 6 months past decompensation had been marked. On June 8, 1915, physical

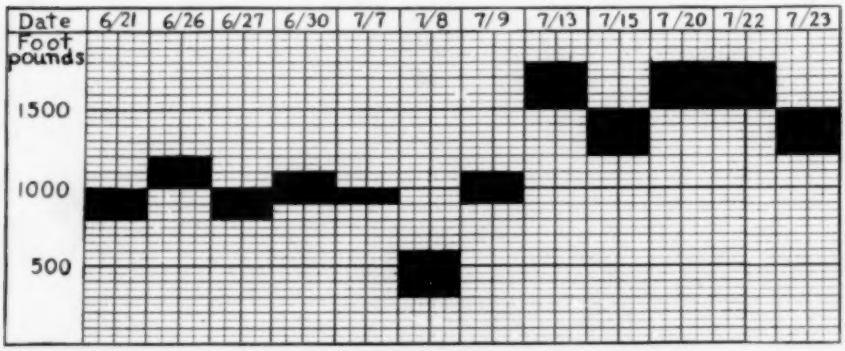

Chart 2.—Course of the heart's capacity in patient C. G., suffering from mitral regurgitation and cardiac insufficiency.

examination showed a pallid man, weighing 192 pounds, dyspneic, and with swollen legs. The heart was decidedly enlarged, regular and rapid in action, and showed a mitral regurgitation. The edge of the liver was felt 6 inches below the free border of the ribs in the midclavicular line. There was also a small amount of fluid in the right pleural cavity. The patient was given 6 drams of tincture of digitalis, and June 21 a course of graduated exercise with dumb-bells and bars was begun. Chart 2 shows the course of the heart's capacity.

On June 21, when the cardiac capacity was 800 foot-pounds in sixty seconds he was able to come to the office daily for treatment, walking two blocks each time. On July 23 he was able to do between 1,200 and 1,500 foot-pounds in sixty seconds and he felt strong enough to go to his own office three times weekly.

The third patient, F. W., was a woman aged 27 years, who for some years had had a mitral regurgitation, with slight enlargement of the heart, but no symptoms of cardiac insufficiency except slight palpitation on exertion. The origin of the heart's condition was unknown. The patient had been careful to avoid physical exertion for several years. She was given a course of graduated exercises.

Chart 3 represents the course of the heart's capacity.

Our experience in estimating the heart's functional capacity by means of dumb-bell movements in a large number of persons suffering

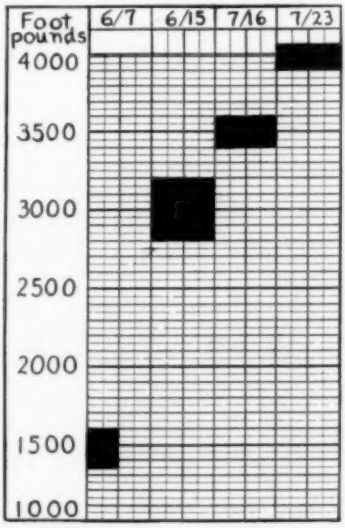

Chart 3.—Course of the heart's capacity in F. W., suffering from well-compensated mitral regurgitation.

from cardiac insufficiency leads us to make the following statements with considerable confidence:

Patients with cardiac capacities under 100 foot-pounds per minute, generally show other signs of cardiac insufficiency. In old people, however, the heart's capacity may be very low and yet no physical sign of cardiac insufficiency be present.

Patients with capacities between 100 and 1,000 foot-pounds per minute are progressively able to be up and about and to do some walking.

A cardiac capacity under 1,000 foot-pounds per minute affords important confirmatory evidence of the existence of suspected myocardial disease.

Although the values of the heart's capacity as estimated in these studies are not absolute, the conception they give us of the heart's function does much to establish a new viewpoint in circulatory physiology.

I am much indebted to Dr. A. C. Sinton and Dr. I. B. Ridgeway, house physicians at the House of Relief, for their help in carrying out the work outlined above.

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THE PRESENT STATUS OF MAGNESIUM SULPHATE IN THE TREATMENT OF TETANUS*

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Ever since the introduction of antitetanus serum by Behring and Kitasato[1] in 1890 there has been more or less increasing disappointment because of the numerous failures after the therapeutic application of this agent. Indeed it was early recognized, even by those who claimed great merit for antitoxin, that in most cases of tetanus it was absolutely necessary to employ other means for the control of violent spasms and the conservation of the patient's strength. Even if, in the end, the serum could neutralize and render harmless the otherwise fatal toxin, it had no immediate effect upon the exhausting and dreaded muscular paroxysms.

Consequently, for the relief of these conditions the attending physician was forced to utilize those sedative and anesthetic drugs, which, in one form or another, have been employed in tetanus ever since the disease has been known. In this, as in other diseases, there would occasionally appear writers whose enthusiastic support for one or the other remedy would, for a time, engender the hope that some really life-saving treatment had been devised, only later to be succeeded by discouragement and therapeutic nihilism as the apparent futility of any remedy whatsoever appeared to have become firmly established. The difficulties in the way of finding the ideal drug were almost insuperable.

The advantages in the use of antitoxins consist chiefly in the fact that their therapeutic effect is obtained without costing the patient one iota of his strength or bodily resistance. In short, for the patient's body, if not for his pocketbook, these remedies are the cheapest known. On the other hand, most antispasmodic and anesthetic agents, such as chloral, opium, chloroform, etc., achieve results by a toxic action and, consequently, for whatever measure of relief the patient obtains, he must pay the price. The more relief he demands, the greater this price becomes until finally the choice must be made as to whether it would be better to die from the toxic action of the disease or from the toxic action of its treatment.

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* From the Department of Pathology, Bacteriology and Public Health, University of Minnesota.

1. Behring and Kitasato: Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Tieren, Deutsch. med. Wchnschr., 1890, No. 49, p. 1113.

Naturally then, when a new drug was proposed or sponsored, it became necessary to examine its merits closely, not only as to its specific therapeutic possibilities, but also as to its comparative freedom from toxic effects. A decision on these points has not always proved to be an easy one and no remedy of modern times has furnished a better example of this fact than has magnesium sulphate[2] in relation to the treatment of tetanus.

When the use of this salt was first proposed it was welcomed with enthusiasm because it apparently possessed many of the required characteristics of an ideal antispasmodic and anesthetic drug. The early belief was in a measure supported by experiments on animals and the successful application to human cases of tetanus in which both the method of use and the therapeutic action were fully illustrated.

It is now ten years since the first report was made by Meltzer and Auer[3] of the use of intraspinal injections of magnesium sulphate in the treatment of experimental tetanus in monkeys, and while, since that time, our knowledge of the limitations and advantages of its use, as well as the various means of its application, has greatly improved, the clinical world today is by no means of a single mind as to the exact place which this drug should occupy in the routine treatment of the disease in man. The extremes vary from those who use it constantly and often report wonderful results to those who refuse to employ it under any circumstances, preferring the more well-known drugs, such as chloral, opium, etc. These extreme views have become especially prominent during the present European war, in which the disease of tetanus has been a frequent scourge and in which every known method of treatment has found both advocates and opponents. In view of all these facts it has seemed worth while to review in some detail not only the development attained in the employment of magnesium sulphate in the treatment of tetanus, with the various methods used, but also to examine the experimental and clinical evidence for its efficiency, and endeavor thereby to arrive at some fair judgment of the future place which should be accorded to the drug in the treatment of this disease.

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2. The magnesium element is, of course, the active agent and theoretically other salts of this metal, namely, magnesium chlorid, might be employed. In fact, Zuelzer (Glycerinphosphorsaures Magnesium als Ersatz für Magnesiumsulfat bei der Behandlung des Tetanus, Berl. klin. Wchnschr., 1915, No. 26, p. 689), has recently suggested the use of magnesium glycerophosphate instead of the sulphate, claiming that it has the efficacy without the dangers of this latter salt. He recommends 10 c.c. of a 25 per cent. solution given subcutaneously every three or four hours.

3. Meltzer and Auer: The Effects of Intraspinal Injection of Magnesium Salts on Tetanus, Jour. Exper. Med., 1906, viii, 692.

THE INTRASPINAL METHOD

Following the recommendations of Meltzer and Auer,[3] who had experimented with magnesium sulphate on eight monkeys and who reported that early intraspinal injections of the salt were capable of retarding the progress and development of tetanus symptoms, most physicians during the first few years of its general use in tetanus, administered it by lumbar puncture. The proof of its usefulness offered by these earlier workers and clinicians was positive and convincing. Not only in monkeys but also in human beings magnesium sulphate could be injected into the spinal canal in such doses as to preserve the respiratory centers, and yet abolish all the clonic convulsions and tonic contractures of tetanic seizures.

A rather careful survey of all the published reports on the occurrence of tetanus in which sufficient details were furnished to admit of classification shows that 81 cases have been described in which the treatment consisted, in part at least, of intraspinal injections of magnesium sulphate. Blake (Table 2, No. 1) in 1906 reported the first case, that of a boy of 15, weighing about 115 pounds (or 52 kilos), who after seven days' incubation period developed a severe attack of tetanus. On the fifth day of the disease he received by lumbar puncture 4.5 c.c. of a 25 per cent. solution of magnesium sulphate (or 0.024 gm. per kilo). The first effects of the salt were noted in less than three hours and in six hours the boy's muscles were so completely relaxed that he could open his mouth and take nourishment. On a return of his symptoms thirty-three hours after the injection, a second dose of 8 c.c. of a 12.5 per cent. solution was given by the same route. In all, the boy received five injections, each one being followed by marked relief and being free from any observable injurious results. Tetanus antitoxin was also freely given and the case ended in complete recovery. Blake (Table 2 No. 2) in this same article, reported the first failure of this new therapeutic procedure, in a case of Dr. Markoe's in which the patient, a boy of 4 years, died twenty-eight hours after the appearance of the first symptoms. The one dose of magnesium sulphate (0.02 gm. per kilo) produced only a slight and transitory amelioration of the spasms.

It only would prove tiresome and also would serve no good purpose to repeat the details of these 81 cases. There may, however, be some value in an analysis of the group as a whole. Thus of the 81 patients, 36 died and 45 recovered, a mortality percentage of 44.4. Of those cases having an incubation period of five days or less (Table 1)—a group which embraces the most severe and almost uniformly fatal cases—6 of the 10 patients treated by intraspinal injections died, a mortality of 60 per cent. Here it must be noted that in one of the fatal cases no antitoxin whatsoever was administered and often only

TABLE 1.—Tetanus Cases Treated by Intraspinal Injections of Magnesium Sulphate: Incubation Period Under Six Days

Author	Publication	Incub. Days	Quantity $MgSO_4$	Anti-toxin*	Result†	Remarks
1. Meltzer and Auer...	Jour. Exper. Med., 1906, viii, 705.....	4	1 c.c. 25% sol. to 18 lbs. body weight	+	X	Complete relaxation. No disturbance of respiration.
2. Peck.....	Reported by Meltzer, 1906.....	4	1 inj. 1 c.c. 25% sol. to 12 kg.	+	X	After $MgSO_4$ all symptoms subsided. Death 2 hours after antitoxin, intravenous.
3. Henry.....	Internat. Clin., 1907, No. 17, Ser. iv, p. 1	3	2 inj. 3 c.c. 25% sol.....	?	0	Excellent results from $MgSO_4$.
4. Rivet, Bricout and Weill	Tribune méd., Dec. 18, 1909.....	5	3 inj. 10 c.c. 25% sol.	+	0	Retention of urine for 8 days.
5. Phillips.....	Proc. Roy. Soc. Med., 1909-10, iii, 29...	3	3 inj. 4 c.c. 25% sol.; 1 inj. 6 c.c. 25 % sol.; 1 inj. 8 c.c. 25% sol.	—	X	The last two days $MgSO_4$ had no effect. No other treatment given.
6. Phillips.....	Proc. Roy. Soc. Med., 1909-10, iii, 29...	1	1 inj. 5 c.c. 25% sol.	?	X	
7. Fox.....	Med. Rec., New York, 1910, lxxviii, 262	5	25 min. 25% sol.	+	0	Attempted second injection of $MgSO_4$ failed.
8. Fox.....	Med. Rec., New York, 1910, lxxviii, 262	5	1 inj. 3 c.c. sat. sol.	+	X	$MgSO_4$ delayed until symptoms became serious.
9. Arnd.....	Cor.-Bl. f. schweiz. Aerzte, 1913, xliii, 106	5	5 inj. 2-3 c.c. 15% sol.	+	0	Failure of respiration. Washed out subdural space.
10. Stromeyer.....	München. med. Wchnschr., 1914, No. 28, p. 1556	4	1 inj. 4 c.c. 10% sol.	?	X	Complicated by pneumonia.

* The sign + = antitoxin given; the sign —, antitoxin not given.
† The sign X = death; the sign 0, recovery.

one dose of magnesium sulphate was given, sometimes late in the disease. One patient (Meltzer and Auer[3]) died while under the influence of the drug, and in another (Stromeyer, Table 1, No. 10) death apparently resulted from respiratory failure and pneumonia two hours after the injection. It is not improbable, however, that most, if not all, of these patients would have died under any circumstances. The number is too small and each case too evidently selected for publication to furnish data on which any certain conclusions may be based. Anders and Morgan,[4] however, in a tabulation of 216 cases collected by them in 1905 present statistics which afford some interesting comparisons (Table 6, Nos. 4 and 5). Of 38 patients having an incubation period of five days or less and not receiving antitoxin 36 died, a mortality of 95 per cent.[5] In the cases of 23 patients with similar incubation but treated by antitoxin 17, or 74 per cent., did not recover.

The second group (that given in Table 2) includes 29 cases with an incubation period of six to ten days and a mortality of 48.6 per cent. Anders and Morgan's cases in this group[4] (Table 6, Nos. 4 and 5) show 58 who received no antitoxin with 79 per cent. mortality. In the 56 cases reported by them in which antitoxin was given 40 patients, or 71 per cent., died. Further reference to Table 6, however, shows that similarly computed end results may show wide variations, which range from 95.6 per cent. mortality (Richter) of such patients without antitoxin, to 73.28 per cent. (Irons[6]), 54.5 per cent. (Chattot[7]), 43.8 (Köhler[8]), and 42 per cent. (Lemonnier[9]) when the serum treatment was used.

In the third group (that in Table 3) with incubation periods over ten days, 29 per cent. of 24 patients died. Here again Anders and Morgan's results[4] (Table 6, Nos. 4 and 5) are significant. In the cases of 18 patients with similar incubation but not receiving serum the mortality was 93 per cent., while of 23 patients treated with antitoxin 35 per cent. died. Irons' mortality[6] for this group is 40.5 per cent.

It becomes readily apparent from all these figures as well as examination of the details of the individual cases, not only that antitetanus serum holds a valuable place in the treatment of all cases of tetanus, whatever the incubation period, but also that the administration of magnesium sulphate by intralumbar injections has brought about a

4. Anders and Morgan: Tetanus, Jour. Am. Med. Assn., 1905, xlv, 314.

5. In Richter's series (Chirurgie des Schussverletzungen im Kriege, 1877, p. 845), a similar group shows a mortality of 96 per cent.

6. Irons: The Treatment of Tetanus by Antitoxin, Jour. Am. Med. Assn., 1914, lxii, 2025.

7. Chattot: Sérothérapie antitétanique, Thèse de Lyon, 1909.

8. Köhler: Zum gegenwärtigen Stand der Serumtherapie des Tetanus, München. med. Wchnschr., 1898, No. 45, p. 1429, and No. 46, p. 1470.

9. Lemonnier: Contribution à l'étude du traitement du tétanos, Thèse de Paris, 1901.

TABLE 2.—Tetanus Cases Treated by Intraspinal Injections of Magnesium Sulphate: Incubation Six to Ten Days

Author	Publication	Incub. Days	Quantity $MgSO_4$	Anti-toxin*	Result†	Remarks
1. Blake	Surg., Gynec. and Obst., 1906, ii, 541	7	2 inj. 4.5 c.c. 25% sol.; 3 inj. 8 c.c. 12.5% sol.	+	0	No injurious results from $MgSO_4$.
2. Blake	Surg., Gynec. and Obst., 1906, ii, 541	7	1 inj. 1.5 c.c. 25% sol.	+	X	Return of convulsions within 1 hour of injection.
3. Logan	Jour. Am. Med. Assn., 1906, xlvi, 1502	9	1 inj. 4 c.c. 25% sol.	+	X	Profuse bronchorrhea.
4. Henry	Internat. Clin., 1907, No. 17, Ser. iv, p. 1	7	1 inj. 6 c.c. 25% sol.	?	X	One hour after injection entirely relaxed.
5. Henry	Internat. Clin., 1907, No. 17, Ser. iv, p. 1	6	1 inj. 2.5 c.c. 25% sol.; 1 inj. 2 c.c. 25% sol.	?	X	Rise of temperature after both injections.
6. Ramond and Doury	Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, 350	6	1 inj. 6 c.c. 25% sol.; 1 inj. 4 c.c. 25% sol.; 1 inj. 3 c.c. 25% sol.	+	0	Recommends $MgSO_4$ highly.
7. Powers	Med. Rec., New York, 1908, xlvii, 146	10	2 inj. 2 c.c. 25% sol.	+	0	Complete relaxation but patient complained of headache.
8. Winthrop	South. Med. Jour., 1909, ii, 916	9	3 inj. 3 c.c. 25% sol.; 1 inj. 3 c.c. 25% sol.	+	0	
9. Willets	Penn. Med. Jour., 1909-10, xiii, 863	7	Injections given for 1 week	+	0	Cyanosis after $MgSO_4$ but was never dangerous.
10. Tanton	Progrès méd., 1909, xxv, 35	8	2 inj. 12-15 c.c. 4% sol.; 1 inj. 3 c.c. 25% sol.	+	X	Relaxation of muscles after $MgSO_4$.
11. Phillips	Proc. Roy. Soc. Med., 1909-10, iii, 39	7	1 inj. 2.5 c.c. 25% sol.; 2 inj. 3 c.c. 25% sol.; 13 inj. 3.5 c.c. 25% sol.	+	0	One injection given daily. No bad effects.
12. Phillips	Proc. Roy. Soc. Med., 1909-10, iii, 39	7	2 inj. 5 c.c. 25% sol.	+	X	
13. Phillips	Proc. Roy. Soc. Med., 1909-10, iii, 39	7	5 inj. 2 c.c. 25% sol.	+	0	Gave $MgSO_4$ because antitoxin and phenol showed no effect.

14. Heineck	Surg., Gynec. and Obst., 1909, No. 1, p. 76	8	6 inj. 5 c.c. 25% sol.	+	0	After first injection rigidity of legs did not return.
15. Hessert	Surg., Gynec. and Obst., 1909, ix, 145	6	1 inj. 3 c.c. 25% sol.	+	X	Death from paralysis of heart.
16. Malanink	Wien. med. Wchnschr., 1909, No. 27, p. 1550	9	2 inj. 2 c.c. 25% sol.	?	X	
17. Holman	Northwestern Lancet, 1911, xxxi, 103	10	2 inj. 5 c.c. 25% sol.	+	X	Failure of respiration after second injection.
18. Petit	Thèse de Paris, 1912	9	2 inj. 3 c.c. 25% sol.	+	X	Good results from $MgSO_4$.
19. Kocher	Cor.-Bl. f. schdeiz. Aerzte, 1912, No. 26, p. 919	7	6 inj. 3-5 c.c. 25% sol.	+	0	After sixth injection, failure of respiration. Tracheotomy.
20. Kocher	Cor.-Bl. f. schweiz. Aerzte, 1912, No. 26, p. 919	10	14 inj. 5-10 c.c. 15% sol.	+	0	After 3 gm. $MgSO_4$, loss of consciousness; cyanosis.
21. Kocher	Cor.-Bl. f. schweiz. Aerzte, 1913, No. 4, p. 97	8	1 inj. 6-10 c.c. 15% sol.	+	0	After 3.5 gm. $MgSO_4$ within 24 hours, failure of respiration; tracheotomy.
22. Kocher	Cor.-Bl. f. schweiz. Aerzte, 1913, No. 4, p. 97	9	6 inj. 2.5-5 c.c. 15% sol.	+	X	Failure of respiration; tracheotomy; death from heart failure.
23. Schoute	Tijdschr. v. Geneesk., 1914, ii, 1839	10	1 inj. 10 c.c. 10% sol.	+	0	
24. Stadler	Berl. klin. Wchnschr., 1914, No. 1, p. 109, No. 3, p. 15	8	8 inj. 2 c.c. 15% sol.	+	0	Several times severe collapse after $MgSO_4$.
25. Stromeyer	München. med. Wchnschr., 1914, No. 28, p. 1556	6	1 inj. 8 c.c. 15% sol.; 1 inj. 8 c.c. 25% sol.	?	0	No failure of respiration.
26. Stromeyer	München. med. Wchnschr., 1914, No. 28, p. 1556	10	1 inj. 8 c.c. 15% sol.	?	X	Died four days after injection from heart failure.
27. Stromeyer	München. med. Wchnschr., 1914, No. 28, p. 1556	6	1 inj. 8 c.c. 15% sol.	?	X	Died day after $MgSO_4$ from heart failure.
28. Goldscheider	Berl. klin. Wchnschr., 1915, No. 10, p. 229	7	1 inj. 2 c.c. 15% sol.	+	X	$MgSO_4$ without effect.
29. Bruce	Lancet, London, 1915, ii, 901	6	3 inj. 2 c.c. 25% sol.	+	0	

* The sign + = antitoxin given; the sign −, antitoxin not given.
† The sign X = death; the sign 0, recovery.

TABLE 3.—TETANUS CASES TREATED BY INTRASPINAL INJECTIONS OF MAGNESIUM SULPHATE: INCUBATION PERIOD OVER TEN DAYS

Author	Publication	Incub. Days	Quantity $MgSO_4$	Anti-toxin*	Result†	Remarks
1. Logan	Jour. Am. Med. Assn., 1906, xlvi, 1502	17	2 inj. 4 c.c. 25% sol.	+	X	$MgSO_4$ of little value.
2. Franke	Zentralbl. f. inn. Med., 1907, No. 14, p. 345	12	1 inj. 1.2 c.c. 25% sol.; 2 inj. 2 c.c. 25% sol.	—	0	Relief from $MgSO_4$ when other narcotics had failed.
3. Henry	Internat. Clin., 1907, No. 17, Ser. iv, p. 1	21	2 inj. 6 c.c. 25% sol.	+	X	"It is very much a question whether the $MgSO_4$ did not contribute to the patient's death."
4. Griffon and Lian	Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, No. 27, p. 190	14	2 inj. 2 c.c. 25% sol.	+	0	Recommends $MgSO_4$ highly.
5. Willets	Penn. Med. Jour., 1909-10, xiii, 863	13	6 inj. 2.5 c.c. 25% sol.	+	0	Relaxation of all muscles after $MgSO_4$.
6. Phillips	Proc. Roy. Soc. Med., 1909-10, iii, 30	38	5 inj. 2 c.c. 25% sol.; 3 inj. 2.5 c.c. 25% sol.; 4 inj. 3 c.c. 25% sol.	+	0	
7. Malanink	Wien. med. Wchnschr., 1909, No. 27, p. 1550	80	4 c.c. 25% sol. every 2 days; 5 c.c. 25% sol. every 3 days	?	0	Good symptomatic influence from $MgSO_4$.
8. Malanink	Wien. med. Wchnschr., 1909, No. 27, p. 1550	14	5 c.c. 25% sol. every 2 days	—	0	
9. Malanink	Wien. med. Wchnschr., 1909, No. 27	11	3 inj. 2 c.c. 25% sol.	+	X	Severe case. Death on fourth day.
10. Goepp and Eshner	Penn. Med. Jour. 1909-10, xiii, 861	20	12 inj. 2 c.c. 25% sol.	+	0	
11. Fox	Med. Rec., New York, 1910, lxxviii, 720	11	1 inj. 2 c.c. 25% sol.	+	0	"Outcome dubious until $MgSO_4$ was given."
12. Johnson	Brit. Med. Jour., 1910, ii, 457	23	2 inj. 45 min. 25% sol.; 2 inj. 1 dr.	+	0	Complete relaxation after each injection.

13. Bertucat.....	Loire med., 1911, xxx, 115.....	60	5 injections	+	0	Chloral and morphin without effect $MgSO_4$ with good results.
14. Holman.....	Northwestern Lancet, 1911, xxxi, 163..	19	9 inj. 10 c.c. 12.5% sol.; 10 inj. 5 c.c. 25% sol.	+	0	
15. Smithson.....	Brit. Med. Jour., 1912, i, 181.....	13	1 inj. 1 c.c. 25% sol.	+	X	For six hours after injection complete relaxation; then high fever with violent spasms.
16. Kocher.....	Cor.-Bl. f. schweiz. Aerzte, 1912, No. 26, p. 919	26	7 inj. 2-5 c.c. 25% sol.	+	0	
17. Kocher.....	Cor.-Bl. f. schweiz. Aerzte, 1913, No. 4, p. 97	28	6 inj. 6-10 c.c. 25% sol. ...	—	0	Failure of respiration; tracheotomy.
18. Tidy.....	Brit. Med. Jour. 1913, i, 1104.....	20-27	3 inj. 3 c.c. 25% sol.	+	0	
19. Spannuth.....	Med. Klin., 1914, No. 46, p. 1688.....	11	6 inj. 25% sol. 0.02 gm. to 1 kg.	—	0	
20. Schoute.....	Tijdschr. v. Geneesk., 1914, ii, 1839...	11	2 inj. 10 c.c. 10% sol.	+	X	
21. Schoute.....	Tijdschr. v. Geneesk., 1914, ii, 1839...	12	3 inj. 10 c.c. 10% sol.	—	0	
22. Vulliet.....	Rev. méd. de la Suisse, 1914, No. 3, p. 185	14	2 inj. 6 c.c. 15% sol.	?	X	Warns that $MgSO_4$ is a two-edged sword and may do more harm than good.
23. Stromeyer.....	München. med. Wchnschr., 1914, No. 28, p. 1556	11	1 inj. 8 c.c. 15% sol.	?	X	Thinks he gave too small doses.
24. Mertens.....	München. med. Wchnschr., 1915, No. 15, p. 534	16	1 inj. 1.5 min. 10 c.c. fluid	+	0	"$MgSO_4$ intraspinally by no means a harmless remedy."

* The sign + = antitoxin given; the sign —, antitoxin not given.

† The sign X = death; the sign 0, recovery.

TABLE 4.—Tetanus Cases Treated by Intraspinal Injections of Magnesium Sulphate: Incubation Period Unknown

Author	Publication	Quantity $MgSO_4$	Anti-toxin*	Result†	Remarks
1. Robinson.....	Jour. Am. Med. Assn., 1907, xxix, 493.....	1 inj. 3 c.c. 25% sol.; 1 inj. 3.5 c.c. 25% sol.; 1 inj. 4 c.c. 25% sol.	—	0	Improvement after $MgSO_4$.
2. Miller.....	Am. Jour. Med. Sc., 1908, cxxxvi, 781.....	11 inj. 2.5 c.c. 25% sol. ...	+	0	Recommends treatment highly.
3. Willets.....	Penn. Med. Jour., 1909, xiii, 863.....	1 inj. 3 c.c. 25% sol.; 2 inj. 4 c.c. 25% sol.	?	0	Artificial respiration necessary for six hours after third injection.
4. Ricard and Dreuet.	Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, xxvi, 189	1 inj. 3 c.c. 25% sol.	?	X	Relief for 24 hours, but spasms returned; death 12 hours later.
5. Roger and Rives...	Province méd. Jour., 1909, xx, 236.....	1 inj. 2 c.c. 25% sol.	+	X	$MgSO_4$ afforded some slight relief.
6 Roger and Rives...	Province méd. Jour., 1909, xx, 236.....	1 inj. 20 c.c. 3% sol.	+	X	Patient died 36 hours after appearance of first symptoms.
7. River, Bricout and Weill	Tribune méd., Dec. 18, 1908, p. 805.....	3 inj. 10 c.c. 25% sol.	+	0	Retention of urine for 10 days.
8. Popesco and Protopesso	Bull. et mém. Soc. méd d. hôp. de Paris, May, 1909, p. 774	1 inj. 4 c.c. 25% sol.; 3 inj. 2 c.c. 25% sol.	+	0	One hour after each injection $MgSO_4$ complete relaxation.
9 Phillips.....	Proc. Roy. Soc. Med., 1909-10, iii, 39.....	6 inj. 2 c.c. 25% sol.	+	0	Gave one injection daily. Good results.
10. Netter.....	Bull. et mém. Soc. méd d. hôp. de Paris, January, 1909, xxvi, p. 151	?	?	X	$MgSO_4$ could not prevent recurrence of spasms or death.
11. Debré.....	Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, Ser. 3, p. 139	1 inj. 2 c.c. 25% sol.	+	X	Excellent effect for 30 hours; then return of symptoms, and death.
12. Aubry and Lerat...	Gaz. méd. de Nantes, May 1, 1909, p. 250.....	3 inj. 25% sol.	?	0	$MgSO_4$ produced positive amelioration.
13. Lenormant and Josset-Moure	Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, xxvi, 431	2 inj. 25% sol.	+	X	No modification of symptoms after $MgSO_4$.
14. Page.....	Proc. Roy. Soc. Med., Jan. 25, 1910, p. 51.....	1 inj. 5 c.c. 25% sol.	?	X	Respiratory failure. "Very dangerous drug."
15. Gardner.....	Austral. Med. Jour., 1911, xvi, 265.....	4 inj. 3 c.c. 25% sol.; 11 inj. 4 c.c. 25% sol.; 2 inj. 2.5 c.c. 25% sol.	+	0	Gave $MgSO_4$ at 18 hour intervals.
16. Smithson.....	Brit. Med. Jour., 1912, i, 181.....	1 inj. 2.5 c.c. 25% sol.	+	X	Failure of respiration but no recurrence of convulsions.
17. Palasse.....	Province méd., 1912, No. 34, p. 375.....	1 inj. 5 c.c. 25% sol.	—	0	High fever and disturbances of circulation after $MgSO_4$.
18. Stadler.....	Berl. klin. Wchnschr., 1914, No. 1, p. 15.....	3 inj. 10.5 and 4 c.c. 15% sol.	+	X	Death from heart failure without asphyxia or convulsions.

* The sign + = antitoxin given; the sign —, antitoxin not given.
† The sign X = death; the sign 0, recovery.

definitely certain, even if small, decrease in the percentage of deaths from tetanus, as well as causing an undoubted diminution in the agony and suffering which accompany the spasmodic seizures of this disease. But our conclusions must not rest here. Further evidence remains to be examined.

THE SUBCUTANEOUS METHOD

In 1907 Greely published a report of the first case to be treated by subcutaneous injections of magnesium sulphate. The salt was given in very dilute solutions (for a child of 2 years, 2 drams to a pint or about 0.57 gm. per kilo) and Greely was unable to determine whether the good results obtained should be attributed "to a dilution of the poisons . . . and an increase in their elimination, to a neutralizing action of the magnesium sulphate on the toxins of the tetanus bacillus, or to its antagonizing effect on the nerve centers."[10]

Meltzer[11] had previously called attention to the efficacy of the subcutaneous method, as well as that of the more rapidly absorbable intramuscular injection.[12]

Lyon (Table 5, No. 3) in the following year added another successful case, and both Hessert[13] and Parker[14] reported recoveries obtained in which the treatment, in addition to antitoxin, consisted of alternating intraspinal and subcutaneous injections of magnesium sulphate. In a comparison by Stadler,[15] 1914, of those cases treated by intraspinal and those by subcutaneous injections of the salt, he also noted the apparently more favorable results obtained by the latter method.

10. Greely is not the only one who has administered the salt under the possible presumption that it might have a specific effect on the toxin and therefore prove a substitute for antitetanus serum. Experiments on animals were carried out, among others by Stadler, Camus (Traitement du tétanos par le sulfate de magnésie, par l'acide phénique, par le sérum antitétanique, Compt. rend. Soc. de biol., 1912, lxxii, 109), and McClintoch and Hutchings (The Treatment of Tetanus, Jour. Infect. Dis., 1913, xiii, 309), with a view of establishing its worth as a *cure* for the tetanus infection. It seems almost needless to add that this presumption rests on no solid foundation of either experimental or clinical proof. Meltzer and his pupils have never claimed that the drug could do more for tetanus victims than to relax the tetanized muscles, thus conserving the patient's strength and gaining time not only for the neutralization of all free toxin by antitoxin but also for the recovery of the nerve centers already affected by their union with toxic elements.

11. Meltzer and Auer: General Anesthesia after Subcutaneous Injections of Magnesium Sulphate, Am. Jour. Physiol., 1906, xiv, 366. Meltzer and Auer: The Antagonistic Action of Calcium on the Inhibitory Effects of Magnesium, Am. Jour. Physiol., 1908, xxi, No. 4, p. 400.

12. This latter method has never been widely employed for administering magnesium salts, probably because of the painfulness of the treatment.

13. Hessert: The Treatment of Tetanus, Surg., Gynec. and Obst., 1909, ix, 145.

14. Parker: Treatment of Tetanus with Magnesium Sulphate, Jour. Am. Med. Assn., 1912, lviii, 1746.

15. Stadler: Die Magnesiumsulfatbehandlung des Tetanus, Berl. klin. Wchnschr., 1914, No. 1, p. 15, and No. 3, p. 109.

TABLE 5.—TETANUS CASES TREATED BY SUBCUTANEOUS INJECTIONS OF MAGNESIUM SULPHATE

Author	Publication	Incub. Days	Quantity $MgSO_4$	Anti-toxin*	Result†	Remarks
1. Greely	Jour. Am. Med. Assn., 1907, xlix, 940..	10	2 inj. 7.5 gm.	+	0	
2. Greely	Jour. Am. Med. Assn., 1907, xlix, 940..	28	3 inj. 3.5 gm.	—	0	Very severe case.
3. Lyon	Jour. Am. Med. Assn., 1908, l, 1688....	8	5 inj. 2 dr. $MgSO_4$ in 4 oz. water	?	0	$MgSO_4$ relaxed muscles to marked degree.
4. Paterson	Lancet, London, April 2, 1910, p. 922	14	10-20 c.c. 10% sol. every 4 hours	—	0	Injections painful but effect of $MgSO_4$ appeared very quickly.
5. Parker	Jour. Am. Med. Assn., 1912, lviii, 1746	7	8 dr. 25% sol. every 2 hrs. first day; 8 dr. 25% sol. daily for one week	+	0	No toxic effects from $MgSO_4$.
6. Parker	Jour. Am. Med. Assn., 1912, lviii, 1746	10	3 inj. 10 dr. 25% sol.	+	0	$MgSO_4$ given daily for 3 days.
7. Mielke	Therap. Monatsh., 1914, No. 4, p. 259	?	15 c.c. 20% sol. for 16 days	+	0	Child did not complain of local pain from injections.
8. Czerny	Deutsch. med. Wchnschr., 1914, No. 44, p. 1905	10	4 inj. 10 c.c. 25% sol.	+	X	Death from pneumonia after tetanic spasms had ceased.
9. Czerny	Deutsch. med. Wchnschr., 1914, No. 44, p. 1905	13	6 inj. 15 c.c. 25% sol.	+	0	Daily injections for 6 days.
10. Czerny	Deutsch. med. Wchnschr., 1914, No. 44, p. 1905	9	10 c.c. 25% sol. daily	+	0	$MgSO_4$ first followed by improvement, later no effect.
11. Roznowski	Ztschr. f. Wundärzte u. Geburtsh., 1914, lxv, 115	4	60 inj. 5-10 c.c. 25% sol.	+	0	From 60 injections only one abscess developed.
12. Heddäus	München. med Wchnschr., 1914, No. 13, 2186	9	10 gm. daily 25% sol.	+	0	Improvement after first injection; later no effect.
13. Syring	Deutsch. med. Wchnschr., 1914, No. 49, p. 2029	20	25 inj. 10 c.c. 10% sol.	—	0	No bad effects from $MgSO_4$.
14. Arzt	Wien. klin. Wchnschr., 1914, No. 52, p. 1683	6	9 inj. 4 c.c. 30% sol.	+	0	

15. Arzt.....	Wien. klin. Wchnschr., 1914, No. 52, p. 1633	6	4 inj. 5 c.c. 30% sol.	+	0	
16. Arzt.....	Wien. klin. Wchnschr., 1914, No. 52, p. 1633	12	4-5 c.c. 30% sol.	+	0	
17. Arzt.....	Wien. klin. Wchnschr., 1914, No. 52, p. 1633	12	4-5 c.c. 30% sol.	+	0	
18. Dreyfus and Unger	München. med. Wchnschr., 1914, No. 51, p. 2417	6-7	2 inj. 5 c.c. 25% sol.	+	0	
19. Dreyfus and Unger	München. med. Wchnschr., 1914, No. 51, p. 2417	6	3 inj. 5 gm. 25% sol.	+	0	
20. Dreyfus and Unger	München. med. Wchnschr., 1914, No. 51, p. 2417	8	6 inj. 5 gm. 25% sol	+	0	
21. Czerney.....	Deutsch. med. Wchnschr., 1914, No. 40, p. 1806	?	3 inj. daily 10 c.c. 25% sol.	+	0	
22. Falk.....	Deutsch. med. Wchnschr., 1914, xl, 1689	?	In 24 hours 4 gm. 10-15% sol.	?	0	After injections, respiration failure 20 minutes.
23. Falk.....	Deutsch. med. Wchnschr., 1914, xl, 1689	?	In 24 hours 3.6 gm. 10-15% sol.	?	0	Continued $MgSO_4$ for 10 days.
24. Falk.....	Deutsch. med. Wchnschr., 1914, xl, 1689	?	In 24 hours 2.1 gm. 10-15% sol.	?	0	Light case; no disturbance of respirations.
25. Usener.....	München. med. Wchnschr., 1914, No. 48, p. 2223	?	15 c.c. 25% sol. every 2 hrs.	?	0	Gave as much as 40 gm. $MgSO_4$ a day.
26. Usener.....	München. med. Wchnschr., 1914, No. 48, p. 2223	?	15 c.c. 40-50% sol. every 2 hours	?	0	Great success.
27. Schlesinger.....	Wien. klin. Wchnschr., 1914, No. 48, p. 1553	?	20 c.c. 25% sol. 3 times daily	?	0	Spasms controlled in ½ to ¾ hour after injection.
28. Reingruber.....	Therap. monatsh., 1915, xxix, 148.....	?	20-25% sol. every 2-3 hrs. until 20-30 gm. of sol. in 24 hrs.	—	0	$MgSO_4$ had instant effect upon spasms.

* The sign + = antitoxin given; the sign —, antitoxin not given.

† The sign X = death; the sign 0, recovery.

Mielke[16] in treating a girl of less than 6 years, for sixteen days gave each day 3 gm. (15 c.c. of a 20 per cent. solution) of magnesium sulphate in divided doses about four hours apart. The doses averaged from 0.5 to 0.7 gm. per kilo of body weight. Far from causing the child painful effects, she was afforded such relief from the tetanic spasms that frequently she pleaded that the interval between the injections be shortened.

The literature gives details of 29 cases (Table 5) in which the patients received, in addition to antitoxin and other treatment, magnesium sulphate administered exclusively by subcutaneous injections. Only one patient (Roznowski, Table 5, No. 11), who recovered, gave an incubation period under six days. In the 12 cases beginning on the sixth to tenth days, inclusive, only one patient died, a mortality of 8.3 per cent. as compared with 48.6 per cent. for the same group treated by the intralumbar method. Of the 6 patients having incubation period above ten days and the 9 patients for whom this period is not stated, all recovered, giving a mortality for the entire group of only 3.7 per cent.[17]

Even admitting that the total number of cases is far too small, that the list is also obviously composed of selected successes, and that the more severe cases of shorter incubation time are noticeable for their absence, the result, nevertheless, is imposing and worthy of the most earnest consideration.

THE INTRAVENOUS METHOD

A third method for the administration of magnesium salts in cases of tetanus deserves mention, more perhaps because of its theoretical than because of its practical bearing. Straub,[18] whose earlier work with magnesium salts was devoted to pharmacological researches on their modes of action, was impressed in experiments with the subcutaneous injections of magnesium sulphate with the short, as well as the variable, duration of the effects obtained by this method. To illustrate, he noted that in a rabbit weighing 2 kilos, 10 c.c. of a 25 per cent. solution, given in a single dose under the skin was sufficient to produce a maximum therapeutic effect lasting about twenty minutes. If, however, that amount was divided into four equal doses injected

16. Mielke: Beitrag zur Behandlung von Tetanus mit Magnesiumsulfuricum, Therap. Monatsh., 1914, No. 4, p. 259.

17. The one patient who died (Czerny: Zur Therapie des Tetanus, Deutsch. med. Wchnschr., 1914, No. 44, p. 1905), had practically completely recovered from tetanus symptoms and death on the twelfth day was said to have been caused by pneumonia.

18. Straub: Experimentelle Untersuchung über Wesen und Aussicht der Tetanustherapie mit Magnesiumsulfat, München. med. Wchnschr., 1915, No. 1, p. 25. Tetanustherapie mit Magnesiumsulfat, München. med. Wchnschr., 1915, No. 10, p. 341.

TABLE 6.—Collected Cases with Comparison of Totals and Mortality Percentages at Varying Incubation Periods

Reported by	Treatment	Total Cases	Per Cent.	Incubation Under 6 Days		Incubation 6-10 Days		Incubation Over 10 Days	
				Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
1. Author	$MgSO_4$ intraspinal	81	44.4	10	60	29	48.6	25	29
2. Author	$MgSO_4$ subcutaneous	27	3.7	..	..	12	8.3	..	..
3. Richter	Without serum	214	88.0	25	96	91	95.6	..	..
4. Anders and Morgan	Without serum	114	78.0	38	95	58	79.0	18	39
5. Anders and Morgan	With serum	102	63.7	23	74	56	71.0	23	35
6. Irons	With serum	225	85.7	..	..	131	73.8	69	40.5
7. Köhler	With serum	...	....	..	..	42	43.8	..	..
8. Chattot	With serum	...	....	..	..	110	54.5	..	..
9. Lemonnier	With serum	176	....	..	..	?	42.0	?	17.6

at fifteen-minute intervals, no effect whatsoever was seen, while, on the other hand, if the four doses were injected into four different places at the same time the animal would die in a few minutes. From this he concluded that the action of magnesium sulphate follows solely from its rapid absorption into the circulation and that the intensity of this action is directly proportional to the amount of concentration which the salt reaches in the blood stream. As the kidneys are the main route for the elimination of the drug, he was able to further establish his contention by measuring the rate of excretion in the urine compared with the duration of the effects. Naturally, the rate of absorption from subcutaneous injections varies within wide limits depending upon site, amount, concentration, etc., and hence the reason for the varying intensities and durations of action.

The logical application of these statements is obvious and Straub[18] proceeded to test it by the continuous injection into the blood of animals of a magnesium sulphate solution in such concentration that the pharmacological effect would be constantly maintained and at such a rate as would approximately equal that of its elimination in the urine. As these tests seemed to demonstrate the value of the method, it remained only to test its application on actual cases of human tetanus, a proceeding which a few months later (1915) Straub was able to report. Four patients were treated with a continuous intravenous flow of a 3 per cent. solution of magnesium sulphate. In the first (a case of light local tetanus) a rate of 100 c.c. in twelve minutes was continued for one hour with no effect. The rate was then increased six times, so that 100 c.c. entered the circulation every two minutes, and typical and satisfactory effects were observed. This observation was repeated on the following day with similar effect and apparently demonstrated that the action of the salt depended solely on its concentration in the blood. The next trial was on a severe case of tetanus in which the first symptoms had appeared eight days after fracture of the arm caused by a bursting shell. The mouth could not be opened, speech was difficult, swallowing impossible, and painful paroxysms of the neck muscles were frequent. After the inflow of a 3 per cent. solution at the rate of 25 c.c. every two minutes, all pain, spasms, and paroxysms disappeared and the patient could talk and drink fluids. One hour after stopping the flow the symptoms began gradually to reappear, to be again controlled by another injection. The interesting observation was made that the muscles affected by the spasms were acted on before the normal muscles and that doses far too small to produce any disturbance of the respiratory centers were sufficiently effective. As the constantly continuous flow proved too great a burden on the circulation (kidneys?), the intermittent method of application was found most suitable. In at least one case the canula was fastened into the vein

and the solution allowed to enter whenever the condition of the patient demanded, for example, for nourishment, changing of dressings, sleep, or too severe muscular spasms. In the case of one patient who recovered this procedure was continued for eight days. The dangers of thrombosis were apparently counteracted by the coagulation-inhibiting properties of the magnesium solution and examination of the veins on necropsy failed to disclose either thrombus or demonstrable injury to the vein wall. Chemical examination of the urine showed that the excreted amounts of magnesium were about equal to the intake.

The actual application of Straub's method in severe cases of tetanus proved disappointing as far as its influence on the eventual outcome of the disease was concerned and its manifest dangers resulted in a suspended judgment as to its true worth.[19]

These experiments have been described in some detail because they undoubtedly illustrate in a very forceful manner not only the theoretical considerations governing the action of this salt but also some of the difficulties which must be encountered in its use, as well as the evident value of its properties in the routine treatment of tetanus.

ACCIDENTS IN THE USE OF THE SALT

As stated above, it must be admitted that, in general, narcotic, anesthetic, or antispasmodic drugs depend on a toxic action for their useful effects, and such effects are always obtained at a distinct cost to part or all of the vital functions of the body. In the use of magnesium salts in tetanus there is considerable evidence which leads to the belief that these are no exception to this general rule. In short, there have been shown, both experimentally and in cases of tetanus, distinct dangers associated with the injections of magnesium sulphate, which dangers must be regarded as an important factor in determining the rightful position which should be accorded to the salt as a remedy. For example, when an overdose of magnesium sulphate in solution is injected rapidly into the blood stream, almost instantaneous death sometimes occurs. This effect is probably brought about by its direct action in concentrated form either on the heart itself or on the cardiac centers of the spinal cord. At any rate the heart suddenly ceases to beat, even before cessation of respiration. As a rule, this misfortune follows only a huge or highly concentrated dose and takes place almost solely as the result of intravenous administration. That such is not always the case, however, was demonstrated on several occasions in a

19. In this connection it should be noted that Meltzer (Meltzer and Auer: Einiges zur Physiologie und Pharmakologie des Magnesium und Kalzium, Deutsch. med. Wchnschr., 1909, No. 45, p. 196), distinctly states that the use of magnesium sulphate in tetanus by intravenous injections should not be considered. ("Intravenöse Einspritzungen sollen beim Menschen gar nicht in Betracht kommen.")

series of experiments in which I was endeavoring to substitute intra-abdominal for intravenous injections of magnesium sulphate in the treatment of experimental tetanus in animals. Large and concentrated doses often led to sudden interruption of the heart's action and this effect was produced almost as rapidly by the intraperitoneal as by the intravenous route. This accident was never observed to follow subcutaneous injections but some reports on patients treated by the intralumbar method suggest strongly that here also there may be a possible danger to the cardiac apparatus. While this accident, when it does occur, has no known remedy, death taking place almost immediately, it must be admitted that, with ordinary precautions, it is not to be expected. Indeed, Meltzer has steadily denied its possibility, asserting that the salt's dangerous action is exerted mainly if not solely on the respiratory centers. However, the above-mentioned facts render necessary further study on this point and in the meantime its use in cases of known cardiac weakness certainly deserves some caution.

The most important and frequent accident resulting from the use of magnesium salts is interference with respiration, that is, respiratory paralysis. This effect apparently is produced by the salt's acting directly on the centers of respiration, and while Meltzer, among others, early demonstrated that tetanized muscles could be relaxed by appropriate doses without endangering the respiration, nevertheless the danger was such a real one that the need for some antidote became at once apparent. Long before magnesium sulphate was proposed for the treatment of tetanus the antagonistic action between the salts of magnesium and calcium had been observed (Loeb[20]). Later Meltzer showed by experiments on rabbits that calcium can remove the inhibiting effect of magnesium. He administered subcutaneously 7 c.c. of a 25 per cent. solution of magnesium sulphate and when the animal was in deep anesthesia and the muscles completely relaxed, injected slowly into the ear vein 6 to 8 c.c. of a 3 per cent. solution of calcium chlorid. In a few moments the respirations became deeper and more rapid, the lid reflex reappeared and the animal attempted to get up, often before the injection was entirely finished. Several minutes later the animal was apparently entirely normal. This effect ensued even when the respirations had entirely ceased, in fact as long as the heart action remained intact. The same result was obtained in experiments on monkeys, and occurred no matter whether the magnesium sulphate had been injected subcutaneously, intramuscularly, or intravenously.

This neutralizing action was not so apparent when the magnesium salt was applied directly to the medulla or the nerve trunks or injected into the subarachnoid space. Hence, for combating its effects after

20. Loeb: Jour. Biol. Chem., 1905-1906, i, 427.

intralumbar injections it was suggested that washing out the subarachnoidal space with physiological salt solution would rapidly relieve the depressent action of the magnesium. Physostigmin was also shown by Joseph and Meltzer[21] to act as an efficient remedy against the threatened respiratory depression of magnesium salts.

Kocher,[22] who was an early champion of the use of magnesium sulphate in tetanus, experienced considerable difficulty with this complication. In some of his early cases he was compelled to perform tracheotomy and even proposed this procedure in severe cases as a routine precautionary measure. He also tested the effect of physostigmin, washing out the intralumbar space with salt solution and tracheal insufflation. He was finally led to recommend that when the salt was injected into the spinal canal, the patient be elevated to a sitting or half reclining position, to prevent its early diffusion to the vital centers. Kocher later (1914) abandoned entirely the intralumbar method in children but intimated that in adults he feared the effect on the heart's action of subcutaneous injections although admitting that in general they were "much milder and less dangerous" than lumbar injections and overdoses could be easily controlled by the use of 5 per cent. solutions of calcium chlorid, or by physostigmin. He proposed a well-known modification of the tracheal insufflation method devised by Meltzer† to aid artificial respiration. It is of interest to note that after a large and varied experience with its use Kocher concluded that in magnesium sulphate we have a most important remedy for preventing the fatal outcome of severe cases of tetanus. Falk[23] among others tested the efficacy of calcium chlorid in respiratory paralysis which appeared in two of his cases and found prompt betterment following *intramuscular* injection of 5 c.c. of a 5 per cent. solution.

I have dwelt on this complication at some length because it constitutes the most serious objection to the use of magnesium sulphate in tetanus. Moreover, this danger seems to be exaggerated when the salt is administered intralumbarly not only because of the possibility of directly diffusing toward higher centers in too great concentration but also because remedies such as calcium chlorid or physostigmin are not so efficient under these circumstances. With subcutaneous injec-

21. Joseph and Meltzer: The Life-Saving Action of Physostigmin in Poisoning by Magnesium Salts, Jour. Pharmacol. and Exper. Therap., 1909, i, No. 3, p. 369.

22. Kocher: Erfolge einer neuren Behandlungsmethode bei Tetanus, Cor.-Bl. f. schweiz. Aerzte, 1912, No. 26, p. 919. Weitere Beobachtungen über die Heilung des Tetanus mit Magnesiumsulfat, Cor.-Bl. f. schweiz. Aerzte, 1913, No. 4, p. 97.

† Meltzer: Pharyngeal Insufflation—A Simple Method of Artificial Respiration, Studies from the Rockefeller Inst., 1913, xvi, No. 6, p. 421.

23. Falk: Zur Behandlung des Tetanus mit subkutanen Magnesiuminjektionen, Deutsch. med. Wchnschr., 1914, xl, 1689

tions, when respirations become embarrassed we are not so helpless. Subcutaneous, intramuscular, or even intravenous injections of calcium chlorid in 5 per cent. solution give prompt and often complete relief. Physostigmin and artificial respiration[24] may also prove efficacious. However, the danger hovers near in every case in which the therapeutic limit is reached and as this limit and the maximum desired effect are often nearly identical, it becomes necessary to watch these patients very carefully after the administration of large doses and make preparations in advance to rapidly administer measures of relief when needed.

The remaining complications cannot be considered as of major importance, but they should be kept in mind and, when possible, prevented. Retention of urine, supposed to be caused by paralysis of the muscles, has often been observed, among others, by Kocher[22] (Table 2, Nos. 19, 20, 21, and 22; Table 3, Nos. 16 and 17), Rivet, Bricout, and Weill.[25] Kocher suggested that the administration of physiological saline under the skin would relieve this condition and, aside from the occasional necessity of catheterization no serious results have been reported. In my experiments with animals this complication has not been noted.

Another objection often raised, especially to subcutaneous injections of the salt, is the supposed painfulness. The evidence in this respect varies. Stadler investigated the subject by making injections into his own tissues of solutions of varying strength. He tried 5.5 per cent. (isotonic), 11 per cent., 22 per cent., 35 per cent., and 50 per cent. solutions and found that, while the 5.5 per cent. and 11 per cent. solutions were less immediately irritating but were later followed by pain, the momentary pain of the stronger mixtures (22 to 50 per cent.) on the other hand, completely disappeared in a short time. He therefore recommended 30 to 40 per cent. solutions, adding that the smaller volume of these injections was in favor of their employment. Mielke[16] also recommended the employment of more concentrated solutions as being less painful. He further suggested the preliminary administration of chloral for the purpose of lessening pain and also to prevent the occurrence of muscular paroxysms during the injections. Falk[23] thought the solution better borne and less painful in dilutions from 10 to 25 per cent. He, however, warned against the painfulness of the injections and advised preliminary small injections of morphin

24. Willets (The Treatment of Tetanus with Subarachnoid Injections of Magnesium Sulphate, Pennsylvania Med. Jour., 1909-10, xiii, 863), in one of his cases, used artificial respiration for six hours with final recovery. He believes such attempts are often abandoned too soon.

25. Rivet, Bricout, et Weill: Deux cas de tétanos traités per la sérotherapie le chloral et les injections intrarachidiennes de sulfate de magnésie, Tribune méd., Paris, Dec. 18, 1909, p. 805.

or novocain. Wiesel[26] also preceded each injection by novocain to relieve the pain. On the other hand, Roznowski (Table 5, No. 11) gave his patient 60 subcutaneous injections, and, except for the development of an abscess after one of the treatments, no pain was felt at the local point of injection.

On the whole there is little doubt that the injections, especially subcutaneous, are apt to be painful. This, however, can be readily controlled by local anesthetics. The concentrated solutions are probably best borne, although in Greely's cases, where a less than 2 per cent. solution was used, no mention is made of distress at the point of injection.

There has been little attention devoted to studies of the actual lesions which may result from the presence of the salt in the subcutaneous or intramuscular tissues. Abscesses and occasional sloughing and gangrene are mentioned, but the absence of secondary infection in these cases was not demonstrated. Reingruber[27] mentions experiments of Ahrens in which comparisons were made in guinea-pigs of the effects of subcutaneous injections of magnesium sulphate, sodium sulphate and sodium chlorid in solutions of different strengths. In twenty-four hours magnesium sulphate caused a slight inflammatory reaction, which, in forty-eight hours, developed into a gangrene more diffuse than that produced by the sodium salts. In all the numerous injections of magnesium sulphate which I have made in rabbits, guinea-pigs, and rats, no gross lesions were observed beyond occasional diffuse hemorrhages. It often happened that as high as six subcutaneous injections of maximum doses of a 25 per cent. solution were given during a single day without evidences of serious lesion or discomfort on the part of the animal.[28]

What may possibly be a more serious complication is the probable action of magnesium salts on the kidneys. Peck in 1913[29] in a study of the urine of cases of magnesium sulphate surgical anesthesia found hyalin casts in three out of five cases, which casts were not present before operation and disappeared after two days. In one case the urine showed traces of albumin also. Gates[30] tested this matter in experiments on dogs and found that sublethal doses of magnesium

26. Wiesel: Bericht über Beobachteten Tetanusfälle, Off. Proto. d. k. k. Gesell. d. Aerzte in Wien., Wien. klin. Wchnschr., Nov. 27, 1914, No. 49, p. 1575.

27. Reingruber: Ueber die Behandlung des Tetanus mit subkutanen injektionen von Magnesium-sulfuricum, Therap. Monatsh., 1915, xxix, 148.

28. Experiments are now being conducted in this laboratory on the local pathologic changes caused by subcutaneous and intramuscular injections of magnesium sulphate.

29. Peck: The Occurrence of Casts in the Urine Following Magnesium Sulphate Ether Anesthesia, Proc. Soc. for Exper. Biol. and Med., 1913-14, xi, 103.

30. Gates: The Experimental Production of Hyaline Casts by Injections of Magnesium Salts, Proc. Soc. Exper. Biol. and Med., 1913-14, xi, 102.

sulphate intramuscularly or intravenously would regularly produce the temporary appearance of hyalin casts in the urine. Neither epithelial or granular casts nor albuminuria were present. In Straub's[18] experiments the large amounts of sulphate solution thrown into the blood stream must have placed an enormous burden upon the kidneys. Careful records of excretion were preserved but there was no mention of casts or albuminuria, although it is not certain that examinations were made for these elements. The subject was deemed of sufficient importance to justify further experimentation, and in conjunction with Dr. Margaret Warwick investigations are being conducted on rabbits and other animals to determine the exact effects of the salt on the kidneys. Definite conclusions have not yet been reached, but some evidence has already accumulated which tends to indicate a slight toxic action on the renal epithelium. This is undoubtedly not of a severe enough grade to justify abandonment of the drug, but certainly continuous watch on the condition of the urine is indicated and in cases with an existing lesion of the kidneys considerable caution must be exercised in its use. The fact that the main, if not the sole, path of elimination is by way of the urine would alone justify such a warning.

There is no evidence that any organic changes are produced by the salt in other structures of the body, such as brain, spinal cord, nerves, or heart muscle and, while no reported investigations have been made along these lines, we may safely assume that in therapeutic doses at least, these structures will not be seriously affected.

USE OF THE REMEDY IN THE PRESENT WAR

No review of this subject would be complete which does not mention the practical application of magnesium sulphate in tetanus seen during the present European war. Wars have always shown a high percentage of tetanus among the wounded and this conflict is no exception to the general rule.

Before prophylaxis was used routinely on all the fronts, many cases of tetanus developed, and while ideal therapeutic studies have been impossible because of the existing conditions, nevertheless there have appeared from time to time many interesting reports which deserve brief consideration. Because of the apparently greater incidence of tetanus in the early part of the war among German soldiers many of these reports have appeared in the German literature. As would be expected, exceedingly variable opinions are expressed. The group of physicians arrayed *against* the use of magnesium in tetanus is an imposing one. It includes such men as Czerney,[31] who, admitting the quieting and pain-diminishing effects, was not convinced it had

31. Czerny: Einleitung in die Kriegchirurgie, Deutsch. med. Wchnschr., 1914, No. 40, p. 1806.

any real value. Angerer,[32] who early abandoned its use, Kreuter,[33] who had lost two cases in spite of the salt, Hochhaus,[34] whose not overenthusiastic comment classes magnesium sulphate as *ein recht brauchbares Mittel,* Müller,[35] Hohmeier,[36] and Goldscheider,[37] all of whom experienced "no certain success" or "no good success," Madelung,[38] who reserves final judgment, and Matthes,[39] who believes its good influence is limited to the first injection.

Other workers are not so pessimistic and some frankly praise the beneficial effects of magnesium. Thus, Eunike[40] tried intralumbar injections up to 10 c.c. of a 10 per cent. solution in eight very severe cases. Four patients recovered, in two the injections having a surprisingly good effect. He states that all complained of a constricted feeling in the lower part of the chest and heart region following the injection, and some suffered from illusions of hearing and hallucinations, which were relieved by morphin. He thinks the magnesium therapy is the best symptomatic method of treatment yet devised. Wiesel[26] studied 12 cases in Eiselberg's clinic in Vienna, using the salt subcutaneously up to 80 c.c. of a 25 per cent. solution in one day and concluded that the combination of magnesium sulphate and chloral gave the best effect of all the narcotics.

Usener,[41] an enthusiastic advocate, used for a patient who was severely affected but who recovered, over 40 subcutaneous injections at intervals of two to four hours. He found 50 per cent. solutions the least painful. No dangerous symptoms appeared. Dreyfus and Unger[42] treated 32 patients with 22 recoveries (mortality 31 per cent.). They attribute their success to large doses of antitoxin and a definite narcosis therapy. This latter consisted of morphin, "luminal" or scopolamin

32. Angerer, A.: Behandlung des Wundstarrkrampfes, München. med. Wchnschr., 1914, No. 45, p. 2226.

33. Kreuter: Ueber einige praktische wichtige Gesichtspunkte in der Tetanusfrage, München. med. Wchnschr., 1914, No. 40, p. 2045.

34. Hochhaus: Erfahrung über die Behandlung des Tetanus, München. med. Wchnschr., 1914, No. 46, 2253.

35. Müller: Einige Ratschläge für die Behandlung des Wundstarrkrampfes, München. med. Wchnschr., 1914, No. 15, p. 2257.

36. Hohmeier: Ueber Behandlung des Tetanus, München. med. Wchnschr., 1915, No. 5, p. 160.

37. Goldscheider: Klinische Beobachtungen über Tetanus im Felde, Berl. klin. Wchnschr., 1915, No. 10, p. 229, and No. 11, p. 268.

38. Madelung: Ueber Tetanus bei Kriegsverwundeten, München. med. Wchnschr., 1914, No. 52, p. 2441.

39. Matthes: München. med. Wchnschr., 1915, No. 5, p. 160.

40. Eunike: Zur Tetanusbehandlung mit Magnesiumsulfat, München. med. Wchnschr., 1914, No. 45, p. 2225.

41. Usener: Indikation für die subkutane Magnesiumsulfatbehandlung des Tetanus traumaticus, München. med. Wchnschr., 1914, No. 48, p. 2323.

42. Dreyfus and Unger: Die kombinierte Antitoxinüberschwemmungs- und Narkosetherapie des Tetanus, München. med. Wchnschr., 1914, No. 51, p. 2417.

(0.0005 gm.) combined with intramuscular injections of magnesium sulphate. They first gave 20 gm. and over per diem but found these were dangerous given intramuscularly and that 20 c.c. of a 25 per cent. solution three times a day were sufficient to control paroxysms. In occasional very severe cases 8 to 10 c.c. of a 15 per cent. solution were injected into the spinal canal. Wienert[43] obtained good therapeutic effects by subcutaneous injections of 10 c.c. of a 40 per cent. solution. Of 40 patients treated only 16 died (40 per cent. mortality). Finally, from an experience with 25 cases Grundman[44] states that magnesium sulphate surpasses all other narcotics in the treatment of this disease.

Reports from the other warring nations are comparatively few in number and meager in details. Feinmann[45] collected 95 cases of tetanus among 66,110 wounded Russians in the hospitals of Dvinsk. Of these 74 patients died (78 per cent.). He saw no good results following the use of either serum or magnesium salts. Derujinsky[46] on the other hand, reports recovery in five out of six cases of tetanus treated with magnesium sulphate. In France Monod[47] reports using for tetanus cases heavy doses of chloral and intraspinal injections of magnesium sulphate with remarkable effects. Schoute[48] saw two recoveries in three cases of tetanus among Belgian soldiers treated with magnesium sulphate by intralumbar injections.

Somewhat more complete is the review of tetanus for the first year of the war in the military hospitals of England, which is given by Sir David Bruce[49] in the *Lancet*. He found records of 231 cases which showed a group mortality of 57.7 per cent. as compared with a mortality of 78.2 per cent. for 179 cases among British soldiers treated in France. Among these, few received treatment with magnesium sulphate. Two patients (Table 2, No. 29) were given 2 c.c. of a 25 per cent. solution intraspinally. In the case of one of these the dose was repeated twice with recovery. Two other patients received similar treatment, one of them 7 c.c. of a 25 per cent. solution. In another case one dose (amount not given) was injected subcutaneously. In

43. Wienert: Zur Therapie des Tetanus, Deutsch. med. Wchnschr., 1915, No. 4, p. 107.
44. Grundmann: Meine Beobachtungen über Tetanus im Frieden und im Felde, Berl. klin. Wchnschr., 1915, No. 8, p. 180.
45. Feinmann: Symptoms and Treatment of Tetanus, Russk. Vrach., 1915, xiv, No. 39, p. 931.
46. Derujinsky: Recovery in Five Out of Six Cases of Tetanus Under Magnesium Sulphate, Russk. Vrach., 1915, xiv, No. 14; rev. in Jour. Am. Med. Assn., 1915, lxv, 1067.
47. Monod: Acad. de méd., Paris, 1915.
48. Schoute: Behandlung van Tetanes traumaticus met inspiutingen van magnesiumsulfat, Wederl. Tijdschr. v. Geneesk., 1914, ii, 1839.
49. Bruce: An Analysis of Cases of Tetanus Treated in Home Military Hospitals, Lancet, London, 1915, ii, 901.

other cases it was given by the mouth and rectum. These details are important as they show how unfair it would be to base judgments on the effect of a drug which was employed with so little recognition of the principles governing its proper use. Of the nine patients treated seven died. The author concludes "that this method of treatment is powerful and not without danger so that great caution ought to be used in its exhibition."

It seems particularly fitting to close this review with a brief reference to the latest "magnesium" article by Meltzer,[50] printed in both the *Berliner klinische Wochenschrift* and the *Lancet*. He first emphasizes the possibility that the cause of death in tetanus may be a direct result of the severe and exhausting spasms and that, by controlling these with magnesium sulphate, the life of the patient is lengthened and thereby his chances of recovery are increased, because of the formation within the body of antitoxin and the ability of the affected nerve cells to return to a normal state. He believes that magnesium narcosis is due to the passing of the magnesium sulphate out of the lymph stream into the free space which contains the points of contact of the branches of two or more neuron systems,[51] where the salt interrupts the conductivity of afferent and efferent impulses through the neurons. Thence arises the narcosis, the analgesia, and the relaxation of muscles. In discussing the various modes of administration, attention is again directed to the following points: The dosage by the intraspinal route should be 1 c.c. of a 25 per cent. solution for every 10 kg. (22 pounds) body weight; the effect of a 25 per cent. solution, which is nearly molecular, is sharper and more certain than that of less concentrated solutions and that there is no clear evidence in the literature showing any toxic action of such injections on the heart; in cases of respiratory disturbance (which in his experience are very infrequent) one needs only to wash out the spinal canal with physiological saline, remembering that calcium chlorid, physostigmin or eserin do not afford relief in this particular method; and, finally in children Kocher's failure with the intraspinal method and Falk's success with the subcutaneous are perhaps due to the more rapid diffusion in the subdural and arachnoidal spaces of brain and cord in children, compared with adults, as well as the more rapid absorption of the salt from the subcutaneous tissues of the former.

The subcutaneous method gives a slower and hence a possible cumulative action, so that small doses frequently repeated are sufficient in many cases to produce a continuous effect. He emphasizes the sharp

50. Meltzer: Magnesiumsulfat bei Tetanus, Berl. klin. Wchnschr., 1915, No. 11, p. 261. Use of Magnesium Sulphate in Treatment of Tetanus, Lancet, London, 1915, i, 4791.

51. This space has been designated by Sherrington the synaptic membrane.

distinction to be made between subcutaneous and intramuscular injections, the latter acting in a much more rapid and hence more toxic manner. Therefore, caution is to be used not to penetrate accidentally too deeply with the injecting needle. The fact is reiterated that magnesium salts energize the anesthetic properties of ether so that a combination of the two in small doses leads to a deep narcosis and relaxation which is of considerable duration. Chloroform and other narcotics do not possess this property to nearly so marked a degree. He states that nephritis contraindicates the method for (at least) surgical anesthesia. Meltzer notes that a signal advantage of the subcutaneous method is the ease of controlling any dangerous effects of the drug. The administration of 1 mg. of physostigmin or eserin (0.0015 gm.), the injection of an isotonic solution (about 2 per cent.) of calcium chlorid into the muscles in doses of about 50 c.c. or into the veins of a 2 per cent. solution in physiological saline up to 500 c.c., being sufficient to remove at once the depressive action of the magnesium salt.

Lastly, in the routine treatment of tetanus Meltzer recommends starting with a subcutaneous injection of 0.3 gm. or 1.2 c.c. of a 25 per cent. solution per kilo (about 10 c.c. for a normal male adult) repeated four times a day. If severe spasms occur, ether should be used and the dose of magnesium increased to 0.5 gm. per kilo (16 c.c. of 25 per cent. solution for adult male). The bladder may need to be emptied by catheterization. In case of danger from respiratory failure one can resort to the remedies mentioned above as well as the application of an Esmarch bandage to hinder absorption of the salt. In desperate cases artificial respiration should be used. If the symptoms are too severe or the subcutaneous injections fail, the intraspinal method is advised. Antitetanus serum should always be used.

To this admirable summary of this subject by Meltzer there is little to add in conclusion. There can be no doubt in the minds of those who review the evidence that in magnesium sulphate we possess a most valuable addition to our armamentarium in the treatment of tetanus. No such imposing array of facts can be brought forward in favor of chloral or allied narcotic agents, even granting their occasionally apparent good effects.

One further point needs emphasis. It is clearly evident that the drug must be used boldly, if its maximum therapeutic effect is obtained, that this bold use is subject to certain dangers, undoubtedly greater in some patients than in others, that these dangers, when threatening, may be rapidly relieved by simple and easily applied measures, and that, therefore, while this salt is being used, the patient must be under continuous expert attendance, with preparations already made to administer, rapidly, restorative remedies. In my studies of the treatment of tetanus both in man and in animals I have been struck by the need of

constantly watching the patient's condition. The disease at its best is a most desperate one and our remedies must be used as soon as possible and their therapeutic limits attained at the earliest possible moment. It is only in this way that good results may be expected in severe cases. We watch a patient under anesthesia, a woman in childbirth, a case threatened with internal hemorrhage. How much more important in tetanus, with almost sure death before us, that we employ our resources to the limit and immediately meet every change with the necessary maximum therapeutic measure!

The treatment of tetanus has not yet reached the ideal stage. Prophylaxis of all dirty wounds is still our surest weapon of defense. However, it is difficult to avoid the conclusion that in outbroken cases, in addition to antitoxic serum, one's duty is sadly neglected if early, vigorous, and continuous efforts are not made to control the spasms, relieve the distress and pain, and give rest and nourishment by subcutaneous injections of magnesium sulphate in amounts large enough and given often enough to bring about the desired results.

THE BASAL METABOLISM IN OBESITY*

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A year ago I reported some observations of the gaseous metabolism in four cases of obesity and one of acromegaly.[1] At present I wish to discuss the findings in these cases somewhat further, and at the same time to report observations on eight new cases.[2]

The object in view has been to determine whether any gross disturbances in the metabolism as shown by the basal gas exchange occur in obesity.

The method has been described in the previous paper and consists, briefly, in the determination of the gas exchange in the *nüchtern* subject, lying prone, in a moderately warm room, and the calculation of the heat production by indirect calorimetry from the oxygen absorption and the calorific value of oxygen for the respiratory quotient obtained.[3]

In judging of the normality of any given metabolism the body surface is unquestionably a better criterion than the body weight. This has been discussed in previous papers.[1, 4]

It was also pointed out that the DuBois linear formula[5] is far more accurate than Meeh's, particularly when one is dealing with obese subjects. Consequently in the present research, as well as in

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1. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, xxvii, 121.

2. I shall take this opportunity to correct three errors in the previous paper. In the first place Mrs. McK.'s height was incorrectly given. It should have been 144.5 cm. In Table 5, page 133, a cipher should be added to the figures for alveolar ventilation. Lastly, an error was made in measuring N. K. This was called to my attention by Dr. DuBois. The subject was not available so I could not remeasure him, but I have calculated his probable area as shown in Table 2 of the present paper. This correction lowers the figure for his metabolism from 43.1 to 36.4 calories per square meter and hour.

3. When the respiratory quotient was below 0.70 the calorific value for 0.70 was used.

4. Means, J. H.: Basal Metabolism and Body Surface, Jour. Biol. Chem., 1915, xxi, 263. In the latter paper, Dr. F. G. Benedict has kindly called my attention to a slight error. The surface area of P. H. P. (page 264, Table 1), by Meeh's formula, should be 2.230 instead of 2.179 square meters.

5. DuBois, D., and E. F.: Measurement of the Surface Area of Man, THE ARCHIVES INT. MED., 1915, xv, 868.

the former, the area of all the subjects has been determind by the linear formula.[6]

In the following tables the metabolism is given both as per kilogram of body weight and as per square meter of body surface.

In order to get a rough idea of the degree of obesity of the various subjects, I have estimated the proper weight for their height from some insurance tables and expressed their excess weight as a percentage. Thus a patient weighing twice as much as he should is considered 100 per cent. overweight.

In my first paper the metabolism was compared with an average figure of 34.7 calories per square meter and hour, which was based on a large series from the literature in which the Meeh formula was used for surface area. At that time I knew that in obese subjects the Meeh formula gave a higher figure than the linear, but did not appreciate that this was likewise true, though to a lesser extent, in persons of normal build. It would have been more accurate had I used as a standard 38.8 calories per square meter and hour, which is the figure I subsequently obtained in a series of normal men and women when using the linear formula.[4] Even this figure is not entirely satisfactory for it does not take into account changes due to age and sex. In a recent paper DuBois[7] has discussed the basal metabolism at various ages, and has plotted a curve of the same, based on a large series of cases of his own and from the literature, the areas being determined by Meeh's formula. This curve shows the metabolism to be highest between the ages of 3 and 6 years, after that to fall fairly rapidly up to 18 or 20, and then to fall slowly through the remaining decades. As my cases of obesity vary considerably in age it will obviously be unfair to compare them all with the same normal figure. In regard to sex also, Benedict[8] has shown that the metabolism of normal men is somewhat higher than that of women of the same height and weight. Bearing the sex and age difference in mind, and starting with my average of 39.6 for normal men between 20 and 30 years of age, I

6. In measuring obese subjects the results obtained by the linear formula are undoubtedly less accurate than in persons of normal build. On Feb. 9, 1916, Dr. F. G. Benedict and I both measured Mrs. McK. Dr. Benedict's measurements gave an area of 2.37 square meters; mine, 2.12 square meters. She weighed at that time 99 kg. The difficulty lies in making the same amount of traction in taking the circumferences, and in locating some of the bony landmarks. Nevertheless the linear formula is more accurate than any other method available, except the actual measurement of casts or molds of the body.

7. DuBois, E. F.: The Respiration Calorimeter in Clinical Medicine, Harvey Lecture, Nov. 27, 1915.

8. Benedict and Emmes: Comparison of the Metabolism of Normal Men and Women, Jour. Biol. Chem., 1915, xx, 253.

have adopted the following standards with which to compare the metabolism of my fat subjects.

Age, Years	Male	Female
13	46	....
15	43.5	....
20–30	39.0	37.0
30–40	38.0	36.0
40–50	36.0	34.0
50–60	35.0	33.0

These standards while to a certain extent arbitrary, are, I believe, fairly near the real average. In choosing them I used DuBois' age

TABLE 1.—METABOLISM DATA—

Subject	Date	Age	Weight, kg.	Height, Cm.	Surface Area Square Meters (Linear Formula)	Percentage "Overweight"	CO_2 per Minute, c.c.*	O_2 per Minute, c.c.*
Mrs. L. L.	8/ 4/15	36	145.3	163.5	2.79	105	227	324
	10/ 6/15	..	144.5	.....	2.78†	...	230	343
	10/11/15	..	141.5	.....	2.75†	...	226	326
	10/16/15	..	139.0	.....	2.73†	...	219	301.5
	10/17/15	..	139.0	.....	2.73†	...	209	314
	10/18/15	..	138.0	.....	2.72†	...	203	305
	10/20/15	..	137.5	.....	2.71†	...	205	309
	11/13/15	..	133.8	.....	2.68†	...	217.5	298.5
	11/20/15	..	132.0	.....	2.66†	90	213	294
Subject's aver. ..	.....	..	.....	.....	.....	...	.....	.....
Mrs. McI.	1/ 7/16	46	127.0	157.5	2.29	95	203	299
Mrs. Sha.	11/ 4/15	30	113.0	155	2.21	80	184	283
	11/14/15	..	107.5	.....	2.15†	...	190	249
	11/26/15	..	106.5	.....	2.14†	...	195	254
	12/17/15	..	102.0	.....	2.10†	60	168	250
Subject's aver. ..	.....	..	.....	.....	.....	...	.....	.....
Miss P. M.	11/ 1/15	..	99	172	2.11	45	209	245
Mr. Z.	12/ 1/15	30	98	167.5	1.99	50	272	278
H. S. (boy).....	9/ 2/15	13	87.6	146.5	1.47	50	189	236
Mr. P. A. M.	10/13/15	24	96	172.5	2.13	40	253	317
Mr. Ch.	9/16/15	54	102	178.5	2.145	30	.....	282

* The figures for CO_2 and O_2 are in all cases the average of three consecutive ten-minute periods on the Benedict apparatus.
† Corrected from original determination on basis of 0.01 sq. m. per kg.

curve, assuming that changes in the metabolism due to age, expressed in terms of Meeh's area, would run parallel with those expressed in terms of the linear formula area.

The clinical data on the new subjects are as follows:

CASE 1.—Mrs. L. L., aged 36. Has had pneumonia twice. Five pregnancies, four of them ending in miscarriage. Positive Wassermann now. Left ovary removed eight years ago, since then there have been neither pregnancies nor catamenia. Her attitude toward sexual matters is normal. She is nearly always thirsty and has a definite polyuria. Some dyspnea on exertion. Her appetite, she says, is very good. She leads a sedentary life. Has always been fat. At 15 years she weighed 190 pounds; at 20, 200 pounds; at 35, 375 pounds. Physical Examination: Enormous obesity, slightly irregular pupils, knee jerks

—ON ALL NEW SUBJECTS

R. Q.‡	Pulse	Calories per Sq. M. and Hour (Linear Formula)	Calories per Kg. and 24 Hrs.	Total Calories per 24 Hours (Basal)	Standard Basal Metabolism for Age and Sex Calories per Sq. M. and Hour	Percentage Deviation from Standard	Remarks
0.70	70	32.6	15.0	2,185	36	— 9.4	
0.69	74	34.7	16.0	2,315	..	— 3.6	
0.69	73	33.3	15.5	2,200	..	— 7.5	
0.70	66	31.0	14.6	2,035	..	—13.9	Started a complete fast today.
0.67	70	32.3	15.2	2,120	..	—10.3§	Second day of complete fast
0.67	70	31.5	14.9	2,060	..	—12.5§	Third day of complete fast
0.66	73	32.0	15.2	2,085	..	—11.1§	
0.73	68	31.5	15.2	2,030	..	—12.5§	Has been on thyroid extract for last 5 days. Started at 3 grains and increased gradually to 12 grains per day
0.72	67	31.1	15.1	1,990	..	—13.6§	Has been on pituitary substance (B. W. & C.) for last 5 days. Started at 8 grains and increased to 24 grains per day
0.69	..	32.7	15.3	.....	..	— 9.2	
0.68	65	36.7	15.9	2,050	34	+ 7.9	
0.65	68	36.1	16.9	1,910	36.5	— 1.1	
0.76	62	33.0	15.8	1,705	....	— 9.6	
0.77	68	33.9	16.3	1,740	....	— 7.1§	Has been on thyroid extract for last 5 days. Started at 1½ grain per day and increased up to 7½ grains per day
0.67	66	33.5	16.4	1,685	....	— 8.2§	No food for 48 hours. Has been on ovarian extract (Armour) for last 5 days. Started at 2 grains, worked up to 16 grains per day
0.705	..	34.5	16.8	.....	....	— 5.5	
0.85	65	33.9	17.3	1,715	37	— 8.4	
0.98	..	40.7	20.5	2,010	38.5	+ 5.7	
0.80	..	46.2	23.3	1,630	46	+ 0.8	
0.80	..	42.9	22.1	2,190	39	+10	
....	..	37.9	19.1	1,950	35	+ 8.3	

‡ It will be noted that in the case of Mrs. L. L., Mrs. I. and Mrs. Sha. the R. Q. is very low. This is undoubtedly due to the fact that these patients were on a very low carbohydrate intake.
§ Not included in averages.

absent, and a large ventral hernia; otherwise negative. Blood, urine, pulse and blood pressure normal. Sugar tolerance: no reduction after 150 gm. levulose; very slight reduction after 200 gm. of levulose. Roentgen-ray Examination: Sella turcica normal.

CASE 2.—Mrs. McI., aged 46. Nothing remarkable about history or physical examination. Normal save for obesity. Had always been stout. Weighed 250 pounds when she was 16 years old. She has always been a heavy eater and is particularly fond of sweets. Has led a sedentary life. At the present time she is passing through the menopause.

CASE 3.—Mrs. Sha., aged 30. Has had two miscarriages and five pelvic operations. The last operation five years ago, at which time all the pelvic organs were removed; there have been no catamenia since. Before that she had been quite thin but following this last operation gained weight rapidly and steadily to the present time. She says that she is not a heavy eater. Leads a fairly active life. Physical Examination: Negative save for obesity. Sugar tolerance: sugar appeared after 150 gm. of levulose.

CASE 4.—Miss P. M. Has been stout since the age of 15, at which time she had a "goiter" without symptoms of hyperthyroidism; neck at that time measured 16 inches. Following this, had some sort of medication by mouth for two years and neck went down to 14 inches. Eats very little, and leads a very active life, yet gains weight steadily. Catamenia started at 13 and have always been regular. Skin is rather dry, but she perspires normally; hair has been falling and getting brittle. Does not feel the cold particularly and is neither nervous nor abnormally placid. Physical Examination: Unimportant except for the obesity.

CASE 5.—Mr. Z. Perfectly healthy medical student of 30; has been gaining weight for the last five years. Says he does not overeat.

CASE 6.—H. S., boy, aged 13. Always has been very fat, as have all his family. Has been well save for numerous upper respiratory tract infections. Eats large quantities of carbohydrate food, and eats continually between meals. Physical Examination: Shows marked obesity; small genitalia (though patient says erection and ejaculation occur); female type of breast; no pubic or axillary hair. Eye grounds and visual fields normal. Roentgen-ray Examination: Sella turcica normal.

CASE 7.—Mr. P. A. M., a normal man of 24. Has been stout since boyhood. Is a fairly heavy eater and takes little exercise.

CASE 8.—Mr. Ch., man of 54. Has been very stout for years; more so five years ago than at present. History and physical examination not remarkable. When first seen had a slight glucosuria which cleared up readily on slight restriction in carbohydrates.

The experimental data on the new subjects are all given in Table 1. In Table 2 the subjects previously reported are compared with the new standards so that they may be used in the discussion of the whole series.

DISCUSSION OF RESULTS

The basal metabolism of each subject has been compared with an appropriate standard for his or her age and sex, and the percentage variation from that standard noted. Table 3 shows the average metabolism of all the subjects in Tables 1 and 2 divided into two groups, one group including the subjects less than 60 per cent. over-

weight, and the other the subjects more than 60 per cent. overweight. In the former group the actual metabolism is only 0.3 per cent. below the average of the standards for the same subjects, and in the latter group the actual is 2.3 per cent. below the standard average.

Taking the series as a whole, then, we may certainly say that there is no characteristic change whatsoever in the basal metabolism even in very extreme cases of obesity. Or, to put it more concisely, extreme obesity may occur in persons with a normal heat production per unit of surface area.

TABLE 2.—Data on Cases Previously Reported

Subject	Age	Weight, Kg.	Height, Cm.	Surface Area Square Meters (Linear Formula)	Percentage Overweight	R. Q.	Calories per Sq. M. and Hour	Calories per Kg. and 24 Hours	Standard Basal Metabolism for Age and Sex. Calories per Sq. M. and Hour	Percentage Deviation from Standard
Mrs. B.	44	179.0	163.0	2.95	160	0.78	35.4	14.0	34	+ 4.1
Mrs. McK.	48	108.0	144.5*	1.86§	120	0.75	34.8	15.0	34	+ 2.3
N. K. ♂....	15	94.0	165.0	2.11†	55	0.76	36.4*	19.6	43.5	—16.3
Mrs. M.	28	87.0	161.0	2.01	30	0.75	31.1	17.2	36	—13.6

* Values corrected since appearance of first paper as explained in text.

† Obtained from area of Mrs. M., a subject of nearly same weight and height, by equation, Area by Meeh of A : Area of A by linear formula = Area by Meeh of B : Area of B by linear formula.

§ This area was obtained by direct measurement of casts of the body as described in DuBois' paper on body surface determination (Note 5). It was for a weight of 93 kg. For 108 kg., 1.96 would be more nearly correct. However, the conclusions regarding the normality of the metabolism would hold in either event.

TABLE 3.—Average Metabolism of All Cases in Tables 1 and 2

Group	Number of Subjects	Calories per Sq. M. and Hour, as Determined Group Average	Calories per Sq. M. and Hour. Average of "Standards" of Individual Members of Group	Variation of Group Average Metabolism Observed, from "Standard" Average
Subjects more than 60% overweight.....	5	34.8	34.9	—0.3%
Subjects between 30% and 60% overweight	7	38.4	39.3	—2.3%

So much in regard to the series as a whole. Individually we can pick several cases that seem to have an abnormal metabolism. Following the Sage Institute investigators I shall consider a metabolism more than 10 per cent. from its appropriate standard as of questionable normality. On looking over the series we find that N. K. and Mrs. M. (Table 2) both have a metabolism more than 10 per cent. below the normal. Reference to the clinical histories of these cases will show

that they both presented some evidence of hypopituitarism. H. S. (Table 1), however, who likewise was thought to be hypopituitary, had a normal metabolism. Mrs. L. L., whose metabolism was sometimes below 10 per cent., also presented some evidence of hypopituitarism in that her sugar tolerance was increased. From all of this we may say that out of a series of twelve obese subjects three showed a slight reduction in basal metabolism, and that all of these three showed some clinical evidence of disturbed internal secretion.

CONCLUSIONS

1. The majority of obese subjects show no alteration in the basal metabolism, as expressed in terms of their surface area, even though the obesity is of a most extreme type.

2. Occasionally a slight reduction occurs and in such cases clinical evidence of disturbed internal secretion is present.

My sincere thanks are due to Dr. D. L. Edsall, Dr. E. F. DuBois, and Dr. F. G. Benedict, all of whom were good enough to read the original manuscript and make many valuable suggestions and criticisms.

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CORRECTION

In the article by Drs. I. H. Levy and J. L. Kantor, entitled "A Clinical Study of Delayed Gastric Emptying," THE ARCHIVES OF INTERNAL MEDICINE, April, 1916, p. 476, in the section on Tone of Stomach, p. 479, the second sentence should read: "This so-called peristolic function of Stiller is impaired in muscular weakness (atony or myasthenia gastrica).